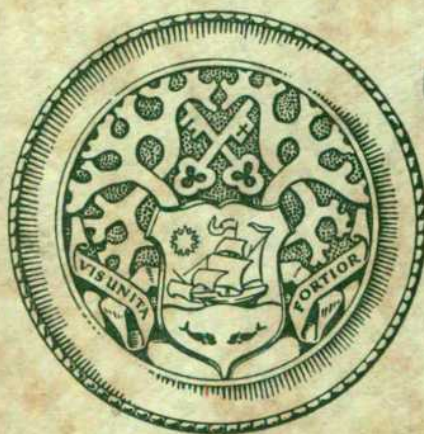


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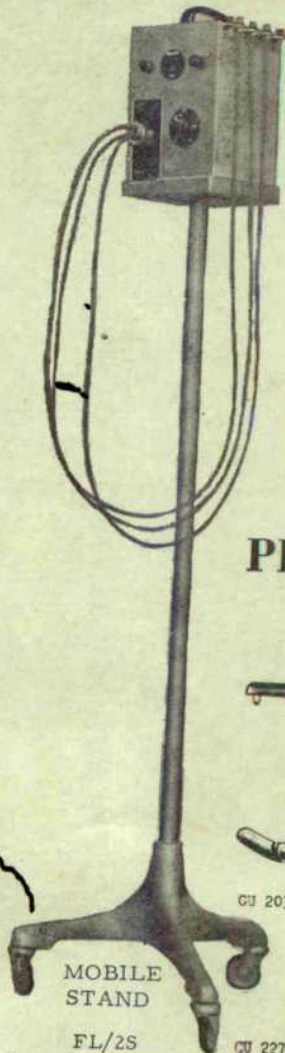
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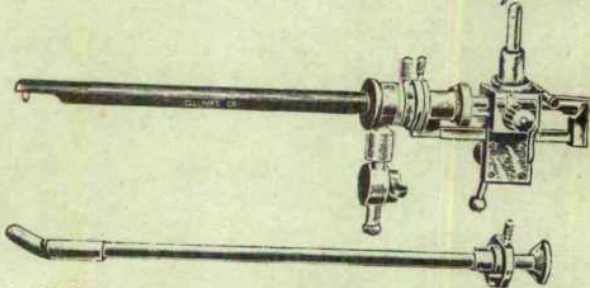
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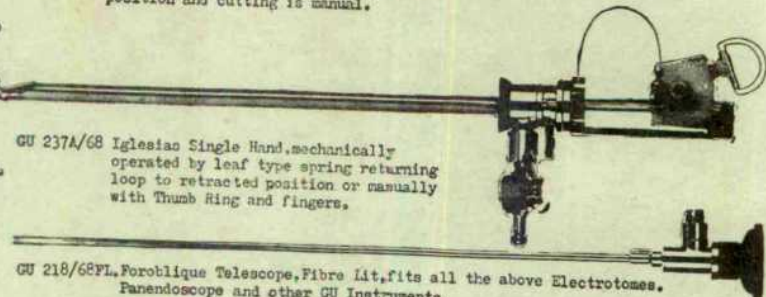


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(1) *Postgrad med J.* (1971), (September Supplement), 47, 7.

(2) *Brit med J.* (1969) *i*, 541.

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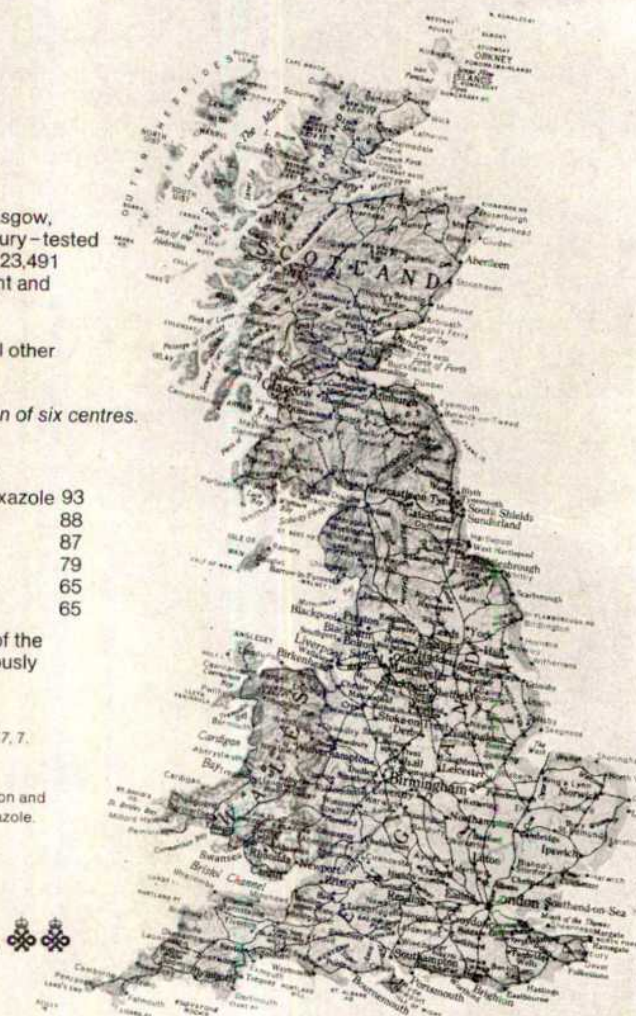
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double blockade of bacterial metabolism
means resistance is unlikely to develop.

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Instructions to Authors

The *British Journal of Urology* welcomes original contributions on urological subjects from all parts of the world. The papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere and that they are subject to editorial revision.

Authors should supply their qualifications, main appointment, and the name and address of the hospital or the laboratory.

Please indicate name and address to which requests for reprints should be made.

Format and content of papers

The text of articles submitted for publication should be typewritten in double-spacing on paper sheet size 22 × 32 cm (A4). There should be a minimum margin of 3 cm all round. The pages should be numbered.

Reports on clinical or laboratory investigation should as far as possible be organised into the following main sections: (1) Introduction, (2) Objective(s), (3) Patients or Materials, (4) Procedures or Methods, (5) Findings or Results, (6) Discussion and (7) Conclusions with (8) a Summary at the end.

Nephrology. Papers on disorders of renal function of interest to the urological surgeon are welcome.

Ethics. When relevant, authors must include a statement on the ethical aspects of their research.

Reports of clinical cases should consist of the following sections: (1) Introduction, (2) Case Reports and (3) Comment with (4) a Summary at the end.

Reports on single cases. Papers reporting a single case are considered for publication as full papers only when the case has definite instructional value. The Introduction and Discussion should not be disproportionate to the case presentation. An abbreviated version suitable for publication as a Short Case Report as an alternative must also be submitted.

In all full papers the literature should be summarised as concisely as is consistent with establishing the necessary basis for new material. Discussions and Conclusions should be strictly limited to the results presented. Recapitulation from previous sections should be avoided whenever possible. Summaries should be composed of very brief statements about each of the main sections.

Headings. The relative importance of sub-headings should be clearly indicated.

Numbers. With the exception of numbers up to 10 at the beginning of a sentence, all numbers should be shown as figures rather than as words.

References. *The accuracy of references is the responsibility of the author.* Only papers closely related to the author's work should be referred to; exhaustive lists should be avoided. *References in the text* should be quoted by the author's name(s) and year of publication. Unless there are more than 3 authors, all the names should be stated at the first reference; if there are more than 3 authors only the first author plus *et al.* is used. In subsequent references to the same paper, *et al.* is used if there are more than 2 authors. *The list of references at the end of the paper* should be in alphabetical order. *References to journals* should include the name(s) and initials of the author(s), year, title of paper, name of journal in full, volume number and the numbers of the first and last pages. *References to books* should include the name and initials of the author, year, title of book, number of edition, city of publication, name of publishing house, and page number(s).

Illustrations. Photographs and radiographs should be submitted in the form of prints on glossy paper of a size no larger than 17.5 × 12.5 cm and no smaller than 9 × 6.5 cm. All figures should be sent unmounted. The number of the figure, the name of the author and the "top" of the illustration should be indicated lightly in pencil on the back. The magnification of micro-photographs should be stated. Graphs and diagrams should be drawn in Indian ink. Legends to figures should be typewritten on a separate sheet of the manuscript. Tables, unless they are very small, should also be typewritten on separate sheets. The position of illustrations and tables should be indicated in the margin of the text.

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Preliminary communications of original work may be submitted as short papers. The communication should be divided into 4 sections: (1) Objectives, (2) Materials and Methods, (3) Preliminary results, (4) Interpretation or Significance of Results.

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Clinicians who have ideas for research projects, but have no opportunity for carrying them out, may submit them for publication in the above section. The communication should not be longer than 500 words. References will be limited to 6.

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Urologists who are willing to undertake abstracting of urological articles appearing in other journals should communicate with the Assistant Editor, Mr W. Selby Tulloch, indicating in which language(s) they are proficient.

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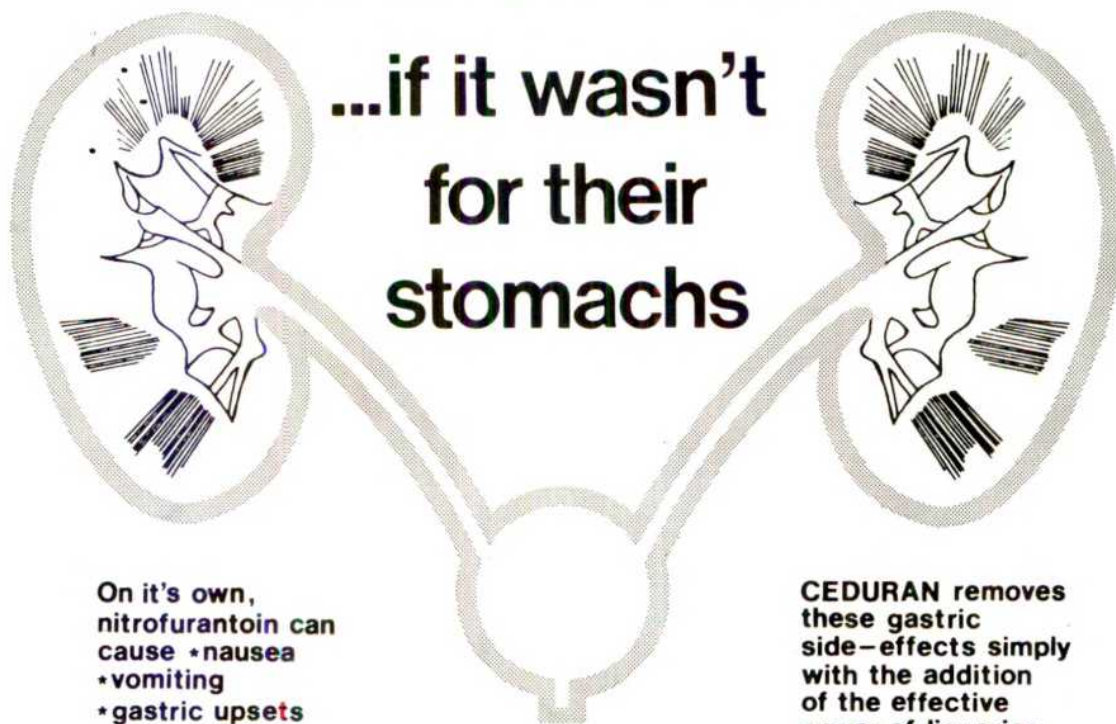
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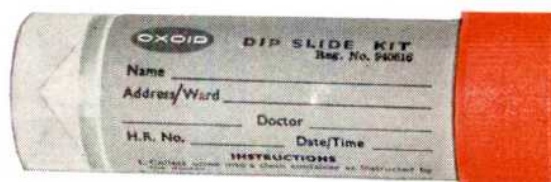
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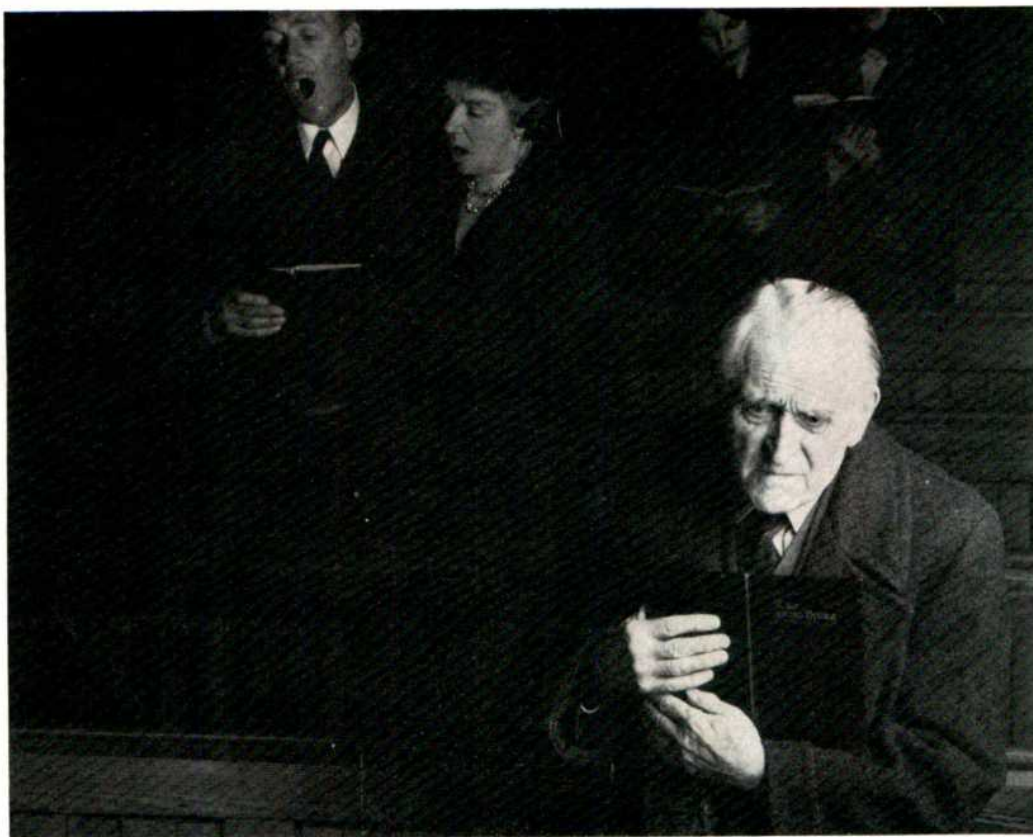
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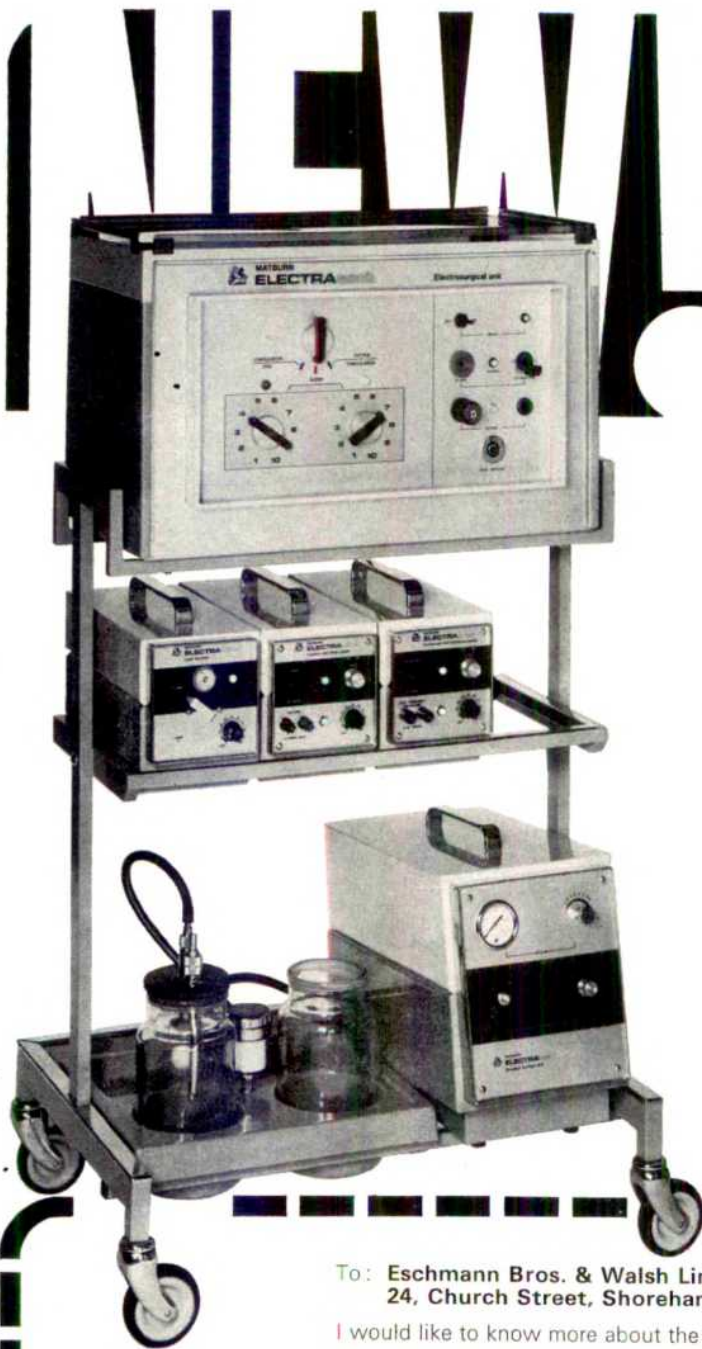
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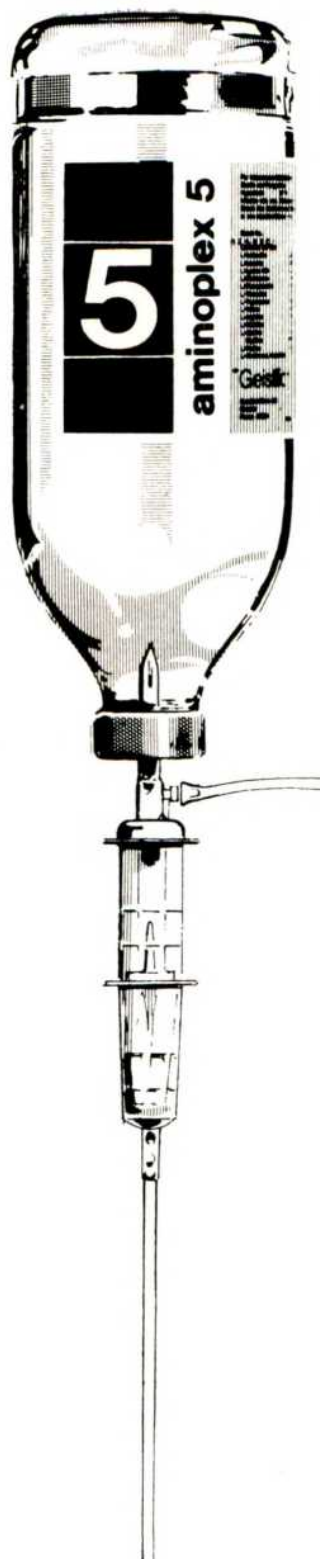
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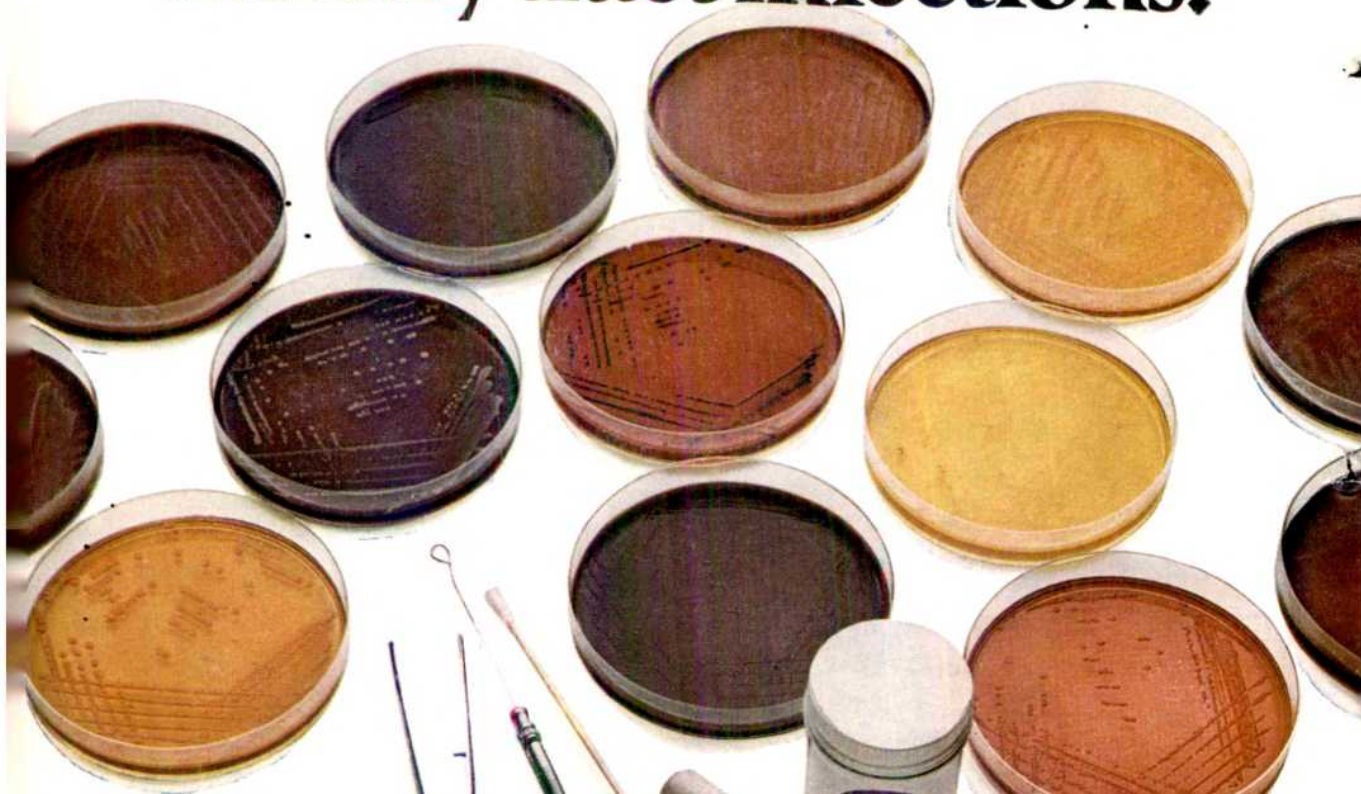
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1. Brit. Med. J., 1972, 3, 13.
2. Brit. J. Clin. Pract., 1972, 26, 341.

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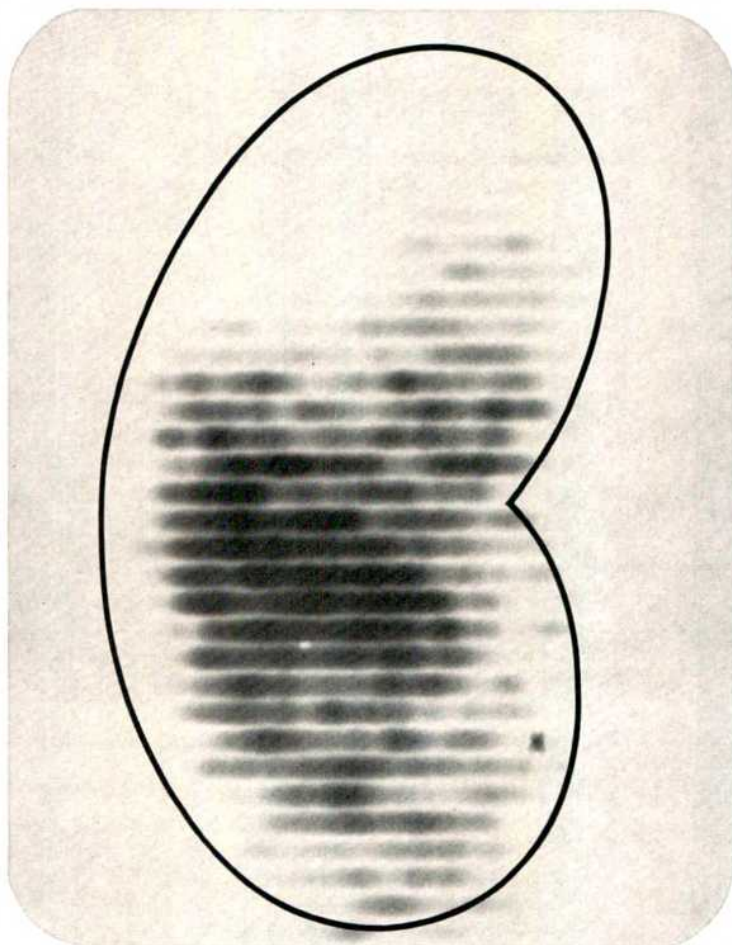
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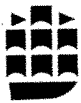
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NEWS FROM HOME AND OVERSEAS

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS

ANNUAL MEETING 1973—*Preliminary Announcement*

At The Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London, WC2A 3PN

President: Mr HOWARD G. HANLEY, M.D., F.R.C.S., F.A.C.S.

The Annual Meeting will be held in London on Wednesday, Thursday and Friday, 27th, 28th and 29th June 1973. A full programme will be circulated later, but the provisional arrangements are as follows:

Wednesday, 27th June

Morning	Registration.
Afternoon	
2.00-4.00	Research Session.
4.30	Annual General Meeting.
Evening	Reception at Chandos House by invitation of the President and Council of the Association.

Thursday, 28th June

Morning and Afternoon	Short Papers.
Evening	Annual Dinner at The Royal College of Surgeons.

Friday, 29th June

Morning and Afternoon	Short Papers.
Evening	A social function will be arranged of which details will be included on the final programme.

Ladies' Programme

It is hoped to arrange a Ladies' Programme.

Hunterian Lecture

A Hunterian Lecture, "Bilateral Renal Calculi", to be given by Professor G. Sreenevasan of Kuala Lumpur, has been arranged at The Royal College of Surgeons on Tuesday, 26th June, at 5 p.m., and Members are invited to attend.

Hotel Accommodation

Members are expected to make their own hotel arrangements and are advised to book early.

Nominations for Council

The attention of members is drawn to the following rule:

"Candidates for the Full Member representatives on the Council shall be nominated by two Full Members at least six weeks before the Annual General Meeting, and shall give their written consent to stand. Candidates for the Associate Member representatives on the Council shall be nominated by two Associate Members at least six weeks before the Annual General Meeting, and shall give their written consent to stand."

Three Full Members and one Associate Member of Council will be retiring in 1973 and nominations for the vacancies must be sent to the Honorary Secretary *not later than* 15th May 1973.

J. P. WILLIAMS,
Honorary Secretary

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON)

A 2-week course under the British Postgraduate Medical Federation's Advanced Postgraduate Training Scheme for N.H.S. Consultants, Senior Registrars and certain Registrars will take place between 2nd and 14th April 1973 at the Institute of Urology, and will be on "Endoscopic Urological Surgery". Further details may be obtained from the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London, W.C.2.

Intra-pelvic Pressure and Renal Function Studies in Experimental Chronic Partial Ureteric Obstruction¹

F. A. W. SCHWEITZER

Guy's Hospital, London

It is well recognised that considerable renal damage may occur with partial ureteric obstruction and that a permanent deterioration of glomerular and tubular function will take place if a complete obstruction exists for longer than 1 week.

However, the changes in function which accompany a partial obstruction—the more usual clinical finding—and the speed of onset have not been adequately studied either in the human or in the experimental animal.

The recent advances in dialysis and transplantation have emphasised the need to preserve functioning renal tissue and the necessity to base timely and accurate surgical treatment on sound evidence.

Historical Review

Numerous workers have performed acute animal experiments, relating the effect of ureteral pressure increase to renal function (Selkurt *et al.*, 1952; Share, 1952; Taylor and Ullman, 1961; Salomon and Lanza, 1962; Malvin, 1964; Fulop, 1970), but the work of Kerr (1954) represented the first attempt to correlate the degree of functional depression in a hydronephrotic kidney of known duration to the recovery which would occur when the complete obstruction was relieved. He found that in these conditions of complete obstruction the only kidneys to return to near normal function were those obstructed for a maximum of 7 days.

In experimental partial ureteric obstruction, produced in a variety of ingenious ways, many investigators (DeLuca *et al.*, 1961; Vaughan *et al.*, 1970) have defined a range of intra-pelvic pressures which may be found and most have confirmed that these pressures tend to fall with time. In the human situation the results are somewhat confusing in that while some workers (Kiil, 1957; Melick *et al.*, 1961) have found a normal intra-pelvic pressure in hydronephrotic kidneys others (Backlund, Grotte and Reuterskiold, 1956; Walzak and Paquin, 1961) were able to show a markedly raised pressure in kidneys whose outflow was obstructed.

Few studies exist which relate the intra-pelvic pressure, under standard conditions of diuresis, during a period of partial obstruction, to the changes in renal function which occur at the same time.

Methods

30 dogs of the Labrador breed housed under identical conditions were involved in this study and were divided into 4 groups, as shown in Table I. Each dog was studied for periods up to 8 months. Group A contained dogs whose renal clearances were estimated as described below and who served as controls with 2 kidneys. Group B dogs underwent a unilateral nephrectomy only, while those of group C had a pressure measuring device inserted into the remaining kidney in

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Table I

GROUPS OF DOGS	
GROUP A	Normal controls.
GROUP B	Unilateral nephrectomy.
GROUP C	Unilateral nephrectomy and insertion of pressure measuring device.
GROUP D	Unilateral nephrectomy, insertion of pressure measuring device and ureteric obstruction.

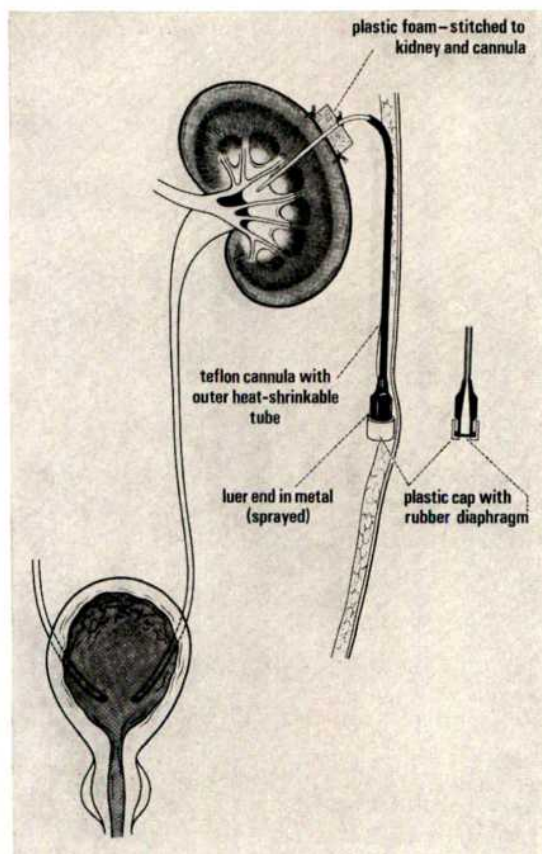


Fig. 1.

addition as described below, and those of group D had their ureter partially obstructed by the method of Ulm and Miller (1962), *i.e.* by burying a segment of ureter in continuity in the psoas muscle of the posterior abdominal wall.

The pressure-measuring cannula consisted of a fine teflon tube with side holes and was inserted into the remaining kidney under general anaesthesia. Details of the method are given elsewhere (Schweitzer, Bowden and Boyd, 1972). Pressure measurement was undertaken by a percutaneous puncture with a serum needle of the proximal end of the cannula, as shown in Figure 1, connected to a strain gauge and a recorder.

Weekly measurement of the glomerular filtration rate using ^{51}Cr ethylenediamine tetra-acetic acid, of effective renal plasma flow using para-amino hippuric acid, of renal concentrating ability using the vasopressin tannate test, and of the blood urea was undertaken. A full range of pressures under all diuretic conditions was also performed each week.

The statistical analysis of the results of the clearances studies is by a process control test, known as the Cumulative Sum Test ("Cusum test") and described in 1958 by Dobben De Bruyn. In this test, which is derived from process control statistics used in industry to monitor a production line, a mean and standard deviation is first described and subsequent results compared to it in a sequential fashion by cumulating the standardised deviation from the mean in a graphical fashion. A V-mask, whose parameters include an amount of bias and a value for p , is laid on the last observation, and if the graph is cut the process has achieved a significant difference from the mean.

In this context we compare the renal clearances in dogs whose ureters are unobstructed, *i.e.* group C to those of group D with obstructed ureters.

Results

Pressure Measurements. 125 separate pressure measurements were taken from dogs in group C to determine the physiological range, and these are presented in Figure 2, from which it can be seen

Table II

RESULTS OF "t" TESTS ON BLOOD UREA ESTIMATION

GROUP COMPARED	"t"	SIGNIFICANCE
B (Unilateral nephrectomy) C (Unilateral nephrectomy and cannulation)	0.9879	No significance
C (Unilateral nephrectomy and cannulation) D (Unilateral nephrectomy, cannulation and ureteric obstruction)	4.2919	$P < 0.001$

that the maximum pressure achieved was 15 mm Hg and that there was in general terms a rise in the intra-pelvic pressure with increasing diuresis.

Figures 3 and 4 show the results of those dogs of group D, *i.e.* those with obstructed ureters, and represent over 400 separate recordings. From this it can be seen that the pressure was directly related to the diuresis and fell to normal levels after a number of weeks. At low levels of diuresis the physiological pressure was rarely exceeded even in the first weeks, while at levels of diuresis up to that which may be regarded as physiological for a dog's kidney the pressure returned to normal in 4 weeks. At high rates and at those forced with an osmotic diuresis it remained high for several more weeks.

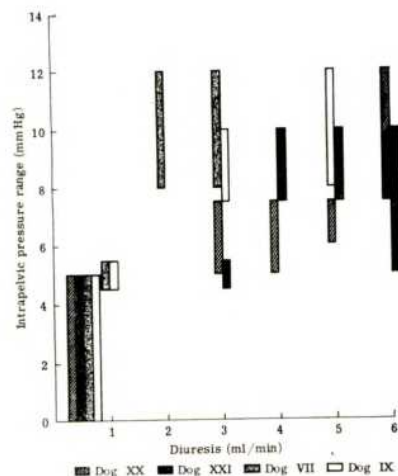


Fig. 2.

INTRA-PELVIC PRESSURES WITH PARTIAL URETERIC OBSTRUCTION

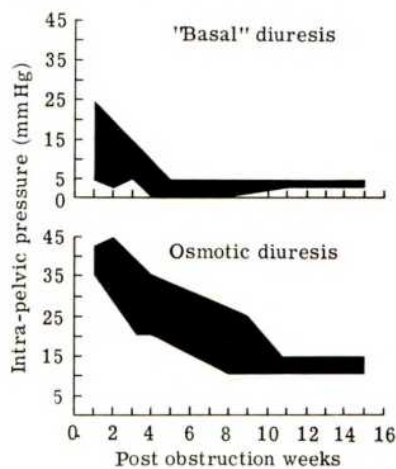


Fig. 3.

INTRA-PELVIC PRESSURES WITH PARTIAL URETERIC OBSTRUCTION

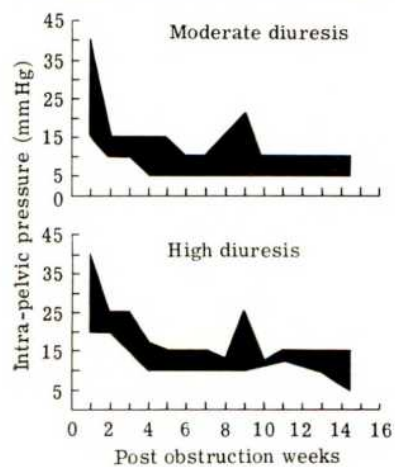


Fig. 4.

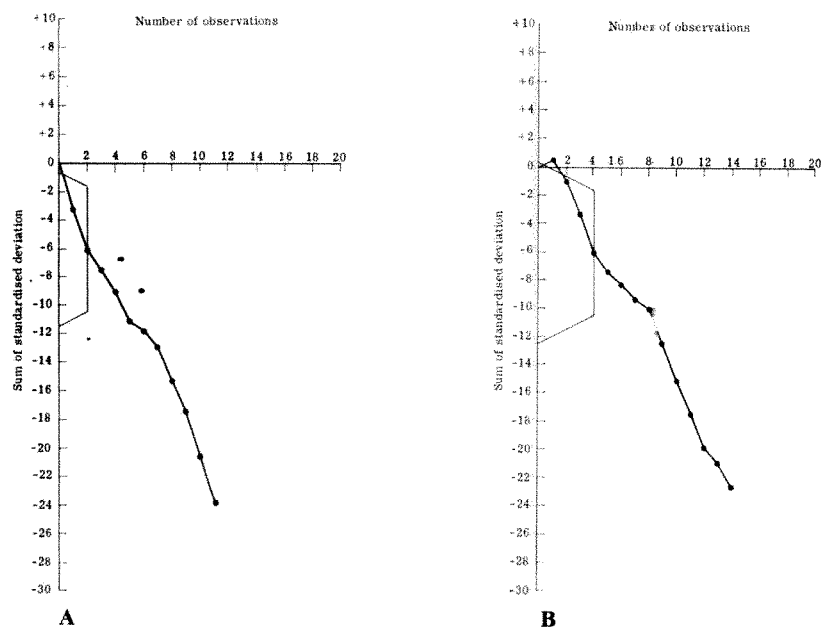


Fig. 5. (A) "Cusum" graph of ^{51}Cr E.D.T.A. clearances of test dog (Group D).
(B) "Cusum" graph of P.A.H. clearances of test dog (Group D).

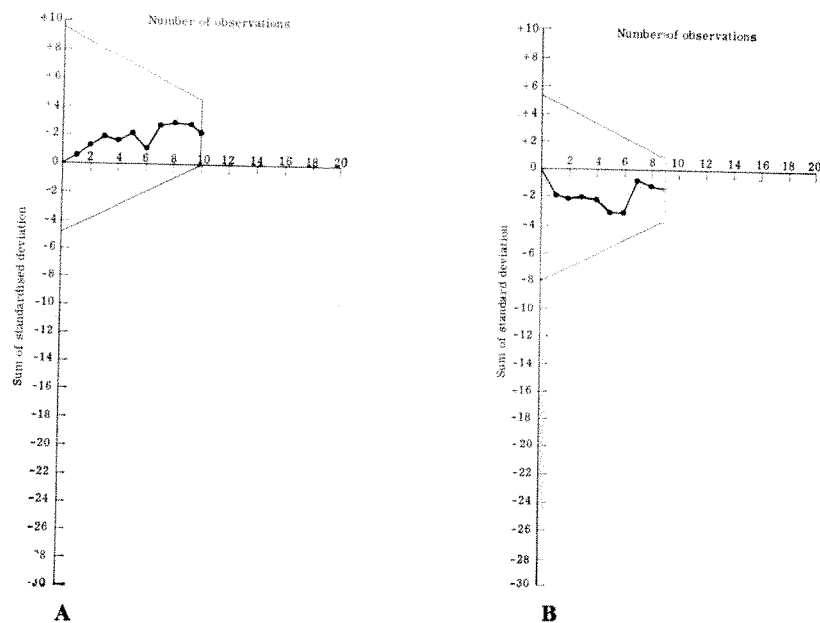


Fig. 6. (A) "Cusum" graph of ^{51}Cr E.D.T.A. clearances of control dog (Group B).
(B) "Cusum" graph of P.A.H. clearances of control dog (Group B).

The conclusion to be drawn is that the physiological pressure is exceeded for 3 to 4 weeks after this degree of obstruction at normal rates of diuresis.

Function Tests. The clearance results are presented as a Cusum graph (Fig. 5) which indicates a significant reduction after a small number of observations when the ureter is obstructed. A similar cusum graph for control animals of group B revealed no similar drop in renal function (Fig. 6).

Moreover, the straightness of the graph implies that there was no continuing drop in the clearances when the line would have become more vertical as the cumulated sum of the deviations increased.

Thus the damage occurs in the early weeks of the obstruction.

The blood urea levels confirmed this reduction in function (Table II).

Conclusions

From the above data it is hard to resist the conclusion that renal damage is produced early in partial ureteric obstruction and is associated with raised intra-pelvic pressures.

If this experimental work can be translated to the human situation the implication must be that surgical intervention of some kind may well be necessary earlier than usually practised if renal damage is to be avoided completely.

It should be remembered that this is a solitary kidney preparation and there is considerable evidence to suggest that the presence of a normal contralateral kidney renders the obstructed one even more vulnerable to damage.

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Spontaneous Extravasation of Urine Secondary to Ureteric Obstruction¹

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Urinary extravasation is most commonly seen following trauma to the renal area. However, with increased use of emergency high-dose urography, spontaneous urinary extravasation has been reported frequently in recent years. The majority of reports have been of few or single cases which has led to confusion in definition, management and prognosis of the condition (Fine and Vermooten, 1960; Hinman, 1961; Smulewicz, 1970; Davidson, 1971). This has led us to review our recent experiences in the Oxford region. We suggest the condition presents in 4 broad clinical groups and consider that the management is governed by the clinical situation supported by the radiological findings and the fact that extravasation *per se* is not necessarily of sinister significance.

Definition and Pathogenesis

Schwartz in 1966 defined the conditions of spontaneous extravasation as urine occurring outside the normal confines of the urinary tract in the absence of recent ureteric instrumentation, previous surgery, external trauma, a destructive renal lesion, urography with external compression or pressure necrosis by stones (Schwartz *et al.*, 1966). We feel that this particularly narrow definition begs the question and that the term "spontaneous" should only exclude cases with a definite traumatic episode, recent instrumentation and urography with external compression.

Extravasation of urine and contrast following obstruction to the outflow tract will occur at the weakest point which may be determined on anatomical grounds (Hamperl and Dallenbach, 1957; Hinman, 1961; Green *et al.*, 1969) or by associated pathological conditions (Hinman and Lee-Brown, 1924; Shaw, 1957; Jeppesen, 1961). The commonest site for extravasation to occur in the previously healthy kidney is a microscopic tear in the calyceal fornix (Hinman, 1961; Schwartz, 1966). This phenomenon occurs in a proportion of acutely obstructed kidneys, though it is only visualised in about 8 per cent of high-dose emergency pyelograms (Schwartz, 1966). Urine may be secreted up to a pressure of 100 mm Hg following obstruction, and extravasation has been shown to occur at varying pressures above 50 mm Hg in the previously healthy urinary tract (Ross, 1959; Elkin *et al.*, 1964). Kiil considers the rate of rise of intraluminal pressure to be an important factor in the production of extravasation (Kiil, 1957).

The presence of previous pathology, such as chronic hydronephrosis, tumour or infection, may either reduce the pressure at which extravasation may occur or change the site producing pelvicalyceal rupture (Hinman and Lee-Brown, 1924; Shaw, 1957; Main, 1967).

It is probable that forniceal tears occur more commonly than they are visualised because obstruction of the ureter both increases the rate of flow of thoracic duct lymph (Chisholm *et al.*, 1967) and the appearance of radio-isotopes in thoracic duct lymph (Murphy *et al.*, 1958). It is therefore possible that forniceal tears represent a normal safety mechanism for the acutely obstructed kidney.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

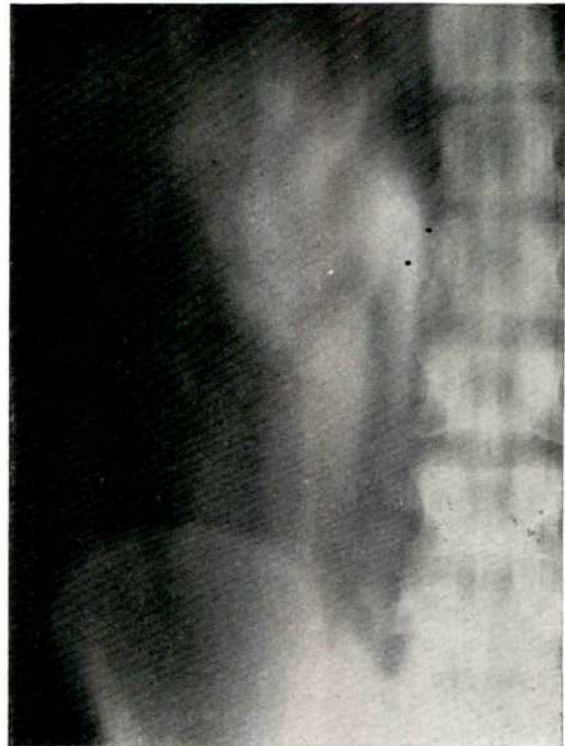


Fig. 1. Case No. 3. Forniceal extravasation following acute ureteric obstruction.

Fig. 2. Case No. 7. Tomogram showing extravasation extending down the ureter, possibly contributing to posterior peritonism.

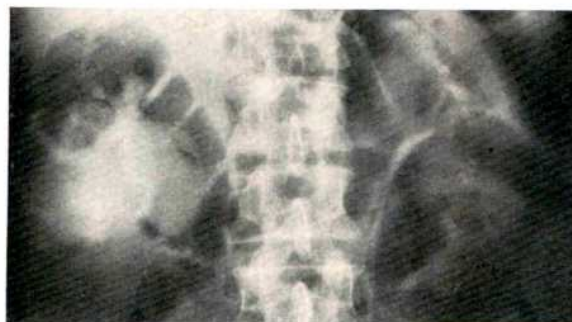


Fig. 3. Case No. 10. Extensive extravasation from the upper calyx, outlining the adrenal gland.

Fig. 4. Case No. 15. Pararenal pseudocyst following chronic calculus ureteric obstruction.

Extravasation may also occur at the site of obstruction, for example erosion of the ureter by a calculus.

Radiology

Emergency high-dose urography has contributed to the increasing frequency of diagnosis. Where obstruction is considered, urography should be performed without abdominal compression. Spontaneous extravasation of contrast will usually be seen earlier in the series than extravasation following abdominal compression (Olsson, 1948; Harrow and Sloane, 1961). Blurring of the psoas outline or meteorism on the plain abdominal film may suggest extravasation. Significant meteorism was seen in 10 of our patients. A soft tissue mass may be shown with pseudocyst formation (Case 13).

Urography may show many of the features of obstruction but, in addition, extravasation occurring from the calyceal fornices and in later films extending through the renal sinus and around the ureter. This type of extravasation was seen in our first group (Fig. 1) and one of our second group of patients (Fig. 2). It is possible that a greater degree of extravasation may be associated with more severe symptoms.

Contrast may, theoretically, enter the renal veins and lymphatics, but this is infrequently seen (Schwartz *et al.*, 1966).

Extravasation following rupture of the renal calyces or pelvis may extend beyond Gerotas fascia, appearing as a dense ill-defined collection of contrast (Fig. 3) (Case 13). This type of extravasation suggests previous renal disease and is associated with the groups of patients requiring surgical treatment.

A well-defined pararenal pseudocyst may be shown by excretion urography (Fig. 4) (Cases 9 and 10) or a paraureteric collection following erosion of the ureter by the stone (Case 12). Retrograde urography is seldom necessary and may occasionally produce extravasation (Ross, 1959; Goldstein and Conger, 1965).

Clinical Presentation and Management

16 patients have been studied, presenting at the Radcliffe Infirmary, Oxford, and Princess Margaret Hospital, Swindon, over 18 months. These patients fall naturally into 4 broad clinical groups, though 2 patients appear in more than 1 group (Table). From these clinical groups it is possible to suggest a pattern of management.

Group 1. These 6 patients in our series, all men, presented as cases of renal colic both on history and physical examination. Micturition disturbance was infrequent, but microscopic haematuria was found in 5 of the 6. All 6 were apyrexial.

The diagnosis was made radiologically in all cases, the extravasation being forniceal (Fig. 1). The diagnosis was confirmed by retrograde pyelography in 1 (Case 3) and by aortography in the first of our series.

In 5 patients calculi were seen while in 1 it was presumed.

The first patient was explored and drained before the benign nature of the condition was fully realised. The remaining 5 were treated with analgesics and fluids. None required further therapy. The majority of reported cases we consider are of this group and may be managed conservatively initially (Fine and Vermooten, 1960; Harrow and Sloane, 1961; Ginsberg, 1965; Rabinowitz *et al.*, 1966; Schwartz *et al.*, 1966; Alexander and Pinck, 1969; Hale and Whitehouse, 1970). Surgical intervention is reserved for persisting symptoms, the appearance of proximal infection and decreasing renal function.

Table

Case	Age	Sex	Clinical Presentation	Presenting T°	Micturition Symptoms	M.S.U.	Means of Diagnosis	Site of Rupture	Treatment	Associated Disease
Group 1										
HM 1	63	M	R. Renal colic	37°	Nil	RBCs +	I.V.P. Aortogram	Fornix	Explored and drained	? Calculus
EM 2	48	M	R. Renal colic	36°	Strangury	RBCs +	I.V.P.	Fornix	Conservative	Calculus and Crohn's disease
AH 3	37	M	L. Renal colic	37°	Nil	RBCs +	I.V.P. + Retrograde	Fornix	Conservative	Calculus
JC 4	24	M	R. Renal colic	37°	Nil	Normal	I.V.P.	Fornix	Conservative	Calculus
RS 5	64	M	L. Renal colic	36°	Nil	RBCs +	I.V.P.	Fornix	Conservative	Calculus
JW 6	61	M	L. Renal colic	37°	Nil	RBCs +	I.V.P.	Fornix	Conservative Failed Dormia extraction	Calculus
Group 2										
DB 7	23	M	Appendicitis	36°	Nil	Normal	(1) Operation (2) I.V.P.	Fornix	Drainage Antibiotics	Calculus
GT 8	34	F	Appendicitis	37°	Nil	Normal	Operation	? Fornix	Ureterolithotomy	Calculus
DW 16	45	F	Cholecystitis	37°	Nil	Normal	Operation	? Pelvis	Laparotomy	P.U.J.O.
Group 3										
IF 9	54	F	R. Renal colic Toxaemia Anuria	38°	Anuria	...	Operation	Fornix	Nephrostomy	Calculus N.F.L. Kidney
JV 10	31	F	L. Renal colic Pyelonephrosis	40°	Nil	RBCs +	I.V.P.	Upper calyx	Pyelolithotomy Drain	Calculus
PR 11	20	M	R. Renal colic Pyelonephrosis	38°	Haematuria	RBCs +	I.V.P. + Retrograde	Lower calyx	Nephrectomy	P.U.J.O.
MR 12	57	F	Pyelonephrosis and Uraemia	39°	Anuria	...	I.V.P.	Fornix	Bilateral Nephrostomy	Ca. Cx. Stage III Ureterocolic anastomosis
TS 13	1/7	F	Urinary retention Ascites	...	Retention	...	Operation Paracentesis	Pelvis	Ureterostomy Nephrostomy, Drain Coag. Valves	Urethral valves
Group 4										
DA 14	62	F	Neurological bladder Pyelonephritis	38°	Strangury	WBCs +	I.V.P.	? Pelvis	Pyeloplasty Excision of cyst	P.U.J.O.
VM 15	62	M	R. Renal colic ? Pyelonephrosis	38°	Haematuria	WBCs +	I.V.P.	? Pelvis	Pyelolithotomy	Calculus
DW 16	45	F	Cholecystitis	37°	Nil	Normal	Operation	? Pelvis	R. Pyeloplasty Excision of cyst	Bilateral P.U.J.O.
IF 9	54	F	Renal colic and Anuria	38°	Anuria	WBCs +	I.V.P. + Retrograde	Ureter	Ureteroureterostomy	Calculus

Group 2. This group we have defined as patients in whom the true diagnosis is missed either because the clinical picture does not suggest urological pathology or because the patient presents with an acute surgical abdomen requiring urgent laparotomy. We have 3 patients in this group, 2 of whom had a history and physical signs compatible with the diagnosis of appendicitis. The third was considered to have acute cholecystitis. None admitted any micturition disturbance and there were no red cells on microscopy of the urine. The correct diagnosis was made in 2 at appendicectomy, when the caecum was found to be floated forward by urine. It is of interest to note that in 1 patient (Case 7) the ureteric calculus was not readily accessible, but following appendicectomy and drainage of the retroperitoneal space the patient's postoperative course was uneventful. Serial intravenous urography confirmed the presence of a calculus with extravasation on the 3rd post-operative day (Fig. 2), thereafter no extravasation was seen but only a mild hydronephrosis. The stone was passed spontaneously a year later. One patient (Case 8) was treated by ureterolithotomy and the third (Case 16) had a diagnosis of hydronephrosis made at laparotomy. This case will be discussed further in Group 4.

In retrospect, the 2 cases subjected to appendicectomy could well have been treated conservatively in the first instance, while in the third more time could have been given for diagnosis. A number of reported cases in the group, however, required urgent surgical treatment because of toxæmia or decreasing renal function usually associated with pelvicalyceal rupture (Clarke, 1955; Jewell, 1964; Main, 1967; Trapnell, 1969). These would naturally fall into our third group when the correct diagnosis is made.

Group 3. Five patients presented in this group with urgent urological problems as a result of their obstruction and extravasation. We have distinguished this group, arbitrarily, from Group 2 on the basis that the diagnosis had been suggested pre-operatively. However, urgent surgery to the renal tract was required because of (a) toxæmia and infection, (b) the severity of symptoms and (c) deteriorating renal function. Four patients were adult while the fifth was a 1-day-old infant. The adults all gave a history suggestive of renal disease, 4 of the 5 had disturbance of micturition function, but the M.S.U. was only abnormal in 2.

All 5 were clinically ill, 2 with anuria, and the neonate with ascites and urinary retention. The 4 adults were toxic.

The diagnosis was confirmed by intravenous urography in 3 patients (Cases 10, 11 and 12) (Fig. 3), 2 of whom showed evidence of pelvicalyceal rupture while the third showed typical mild forniceal extravasation.

The neonate (Case 13) and the remaining adult (Case 9) had insufficient renal function to demonstrate extravasation, but it was confirmed at surgery.

The clinical situation of all 5 patients was such that urgent surgery was necessary to drain the extravasated urine and relieve the obstruction. A nephrostomy tube was inserted in 3 patients (Cases 9, 12 and 13) accompanied by drainage in 2 (Cases 9 and 13) and coagulation of urethral valves in the neonate. The other 2 patients required pyelolithotomy and nephrectomy respectively (Cases 10 and 11) (Table). Four made uneventful recoveries while Case 9 went on to produce a ureteric rupture from erosion of the stone and will be discussed in the fourth group.

Group 4. The 4 patients grouped together presented with chronic renal tract problems and exacerbation of the symptoms, who, on investigation or at operation, were found to have extravasation of urine. The length of history varied from 6 weeks to 3 years, with recent increase in the severity of symptoms. In Case 9 this was associated with decreasing renal function in the presence of a non-functioning left kidney. Three had disturbance of micturition and 3 had pyuria.

The diagnosis was confirmed on excretion urography (Fig. 4) in 3 while the fourth showed hydronephrosis (Case 16). The extravasated contrast entered well-defined cystic spaces in all 3 with apparent communication to the pelvis in 2 and the ureter in 1 (Case 9). The encysted extravasation was associated with chronic distal obstruction but required treatment because of

increased symptoms, the possibility of proximal infection (Cases 14, 15 and 16) and failing renal function (Case 9).

All 4 were treated surgically, with excision and drainage of the encysted urine, and the relief of the obstruction. All made uneventful recoveries.

Discussion

Nine of our 16 cases showed forniceal extravasation following acute calculus obstruction of a previously normal kidney and only 1 required surgery (Case 9). This is in agreement with the majority of reported cases of forniceal extravasation (Fine and Vermooten, 1960; Harrow and Sloane, 1961; Ginsberg, 1965; Rabinowitz *et al.*, 1966; Schwartz *et al.*, 1966; Alexander and Pinck, 1969; Hale and Whitehouse, 1970) though some authors advocate extraction of the calculus (Hinman, 1961).

Extravasation of urine may lead to difficulty in diagnosis either as a result of the extent of a forniceal leak or, more likely, as a result of rupture of the pelviureteric system in association with previous disease (Jewell, 1964; Clarke, 1955; Main, 1967; Trapnell, 1969). It is therefore necessary to consider the diagnosis of urinary extravasation in cases with an acute abdomen, for some may be treated conservatively while others require urgent surgery (Group 3) (Abeshouse, 1935; Forsythe *et al.*, 1958; Jeppesen, 1961; Swain *et al.*, 1965; North *et al.*, 1966; Remzi and Bayraktar, 1967; Smulewicz *et al.*, 1970; Davidson, 1971).

Infection and failing renal function are pressing reasons for surgical intervention in the presence of extravasation. Delay may be fatal (Smulewicz *et al.*, 1970). In these cases the extravasation may be either forniceal or due to pelviureteric rupture.

Extravasation may exist as a chronic condition for months or years as a pararenal or paraureteric pseudocyst before presenting for surgical treatment. Surgery becomes necessary because of increasing symptoms or the appearance of proximal infection. The majority of pararenal pseudocysts are reported to follow trauma, though this is often slight (Arnold, 1971).

Treatment of patients with extravasation depends on their clinical state. The majority may be treated conservatively, but some require either emergency or elective surgery. Emergency high-dose urography is a valuable means of diagnosis, and of showing associated pathological processes.

Summary

16 patients with spontaneous urinary extravasation are presented. It is suggested that they fall into 4 clinical groups and that surgical treatment is governed by the clinical picture supported by the radiological appearances.

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Methods of assessing Obstruction in Dilated Ureters¹

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There are many situations in both paediatric and adult urology where the upper urinary tract is dilated in the absence of reflux and obstruction is suspected. It is wrong, however, to assume that dilatation necessarily indicates obstruction, as there may be a primary defect in the musculature of the ureter (Fig. 1). For instance, in the Prune Belly or the Megaureter-Megacystis syndromes there is usually gross dilatation and often no obstruction.

More difficult to interpret is the degree of dilatation that remains after relief of obstruction. The renal pelvis notoriously remains dilated after pyeloplasty, no doubt due to permanent changes in the musculature, and probably for the same reason, restoration of a completely normal ureteric lumen is seldom obtained after reimplantation of a ureter for obstruction at its lower end.

It is in such situations that there is a need for a test to determine whether or not a dilated upper tract is in fact obstructed. Such a combined urodynamic and radiographic test has been used for the past 2 years at The St Peter's Group of Hospitals, The Hospital for Sick Children, Great Ormond St, and The London Hospital in patients with dilated upper tracts but with no vesico-ureteric reflux and is the subject of this report.

Methods

The principle of the test is to perfuse the whole or part of the upper urinary tract at a constant flow rate with saline or contrast medium from above downwards. This is done through a tube, cannula or needle, and simultaneously the pressure is measured within the renal pelvis or ureter through the same channel. Thus the pressure which is recorded is that pressure necessary to drive the fluid through the system at a fixed flow rate and it takes into account the resistance offered by the tubing and the needle. This arrangement has the distinct advantage of needing only one point of access to the renal pelvis or ureter, and this access is always above the site of the suspected obstruction. This is clearly superior to using a ureteric catheter which must pass retrogradely through the site of the obstruction and itself represents an additional obstruction.

In practice the perfusion is performed by 1 of 3 routes.

1. Nephrostomy Tube. If a nephrostomy tube is already in place it provides easy access to the renal pelvis (Fig. 2). The tube itself is wide and offers no resistance to the flow of fluid.

2. Percutaneous Puncture. The dilated calices or renal pelvis present a relatively simple target for percutaneous puncture (Fig. 2). The needle or cannula should be as wide (at least 18 g) and as short as possible so that its resistance is low, but the actual length will be determined by the size

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

of the patient. Medicut (argyle—18 g × 2 in) intravenous cannulae are suitable in children. It is best to enter the urinary system via the renal substance to give a watertight seal.

Ureters dilate because—

1. They are intrinsically defective.
2. They are, or have been obstructed.

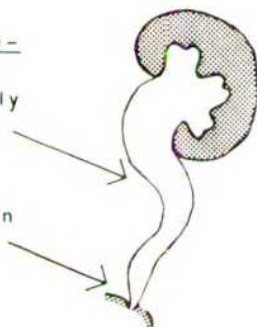


Fig. 1.

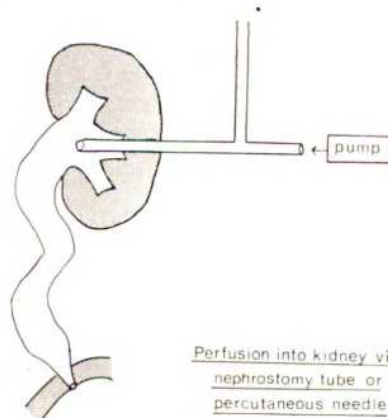


Fig. 2.

The procedure should be done in the X-ray department with the patient prone and either sedated or anaesthetised. A standard dose of contrast medium is given, as for an intravenous pyelogram, to provide a target on the image intensifier which can then be aimed at with the needle. In the grossly dilated system this is unnecessary.

With a percutaneous puncture or nephrostomy tube a small urethral catheter is inserted into the bladder to allow drainage throughout the test and measurement of the bladder pressure at the conclusion.

3. Lower end of the Ureter. During surgical exploration the lower ureter can be isolated outside the bladder and its lumen occluded as high up as possible with a soft-shod occlusion clamp. A

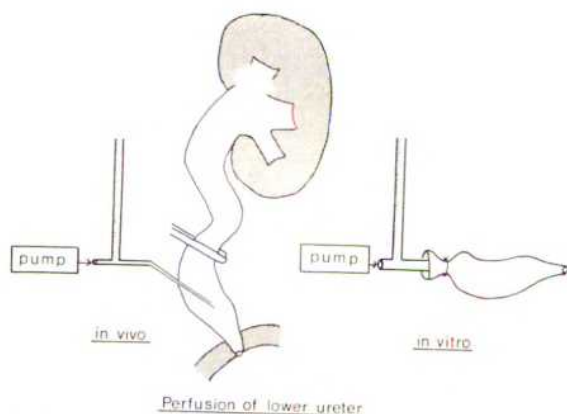


Fig. 3.

needle is then introduced into the lumen of the ureter below the clamp and the isolated lower end of the ureter is perfused (Fig. 3). The bladder is open throughout so that fluid does not accumulate and the pressure remains atmospheric.

A piece of excised ureter can be perfused *in vitro* and the results compared with those of the *in situ* study.

The perfusion is commenced at a fixed high flow rate of 10 ml/min and maintained until the pressure becomes constant (Fig. 4, A). When this equilibrium is reached the whole system is

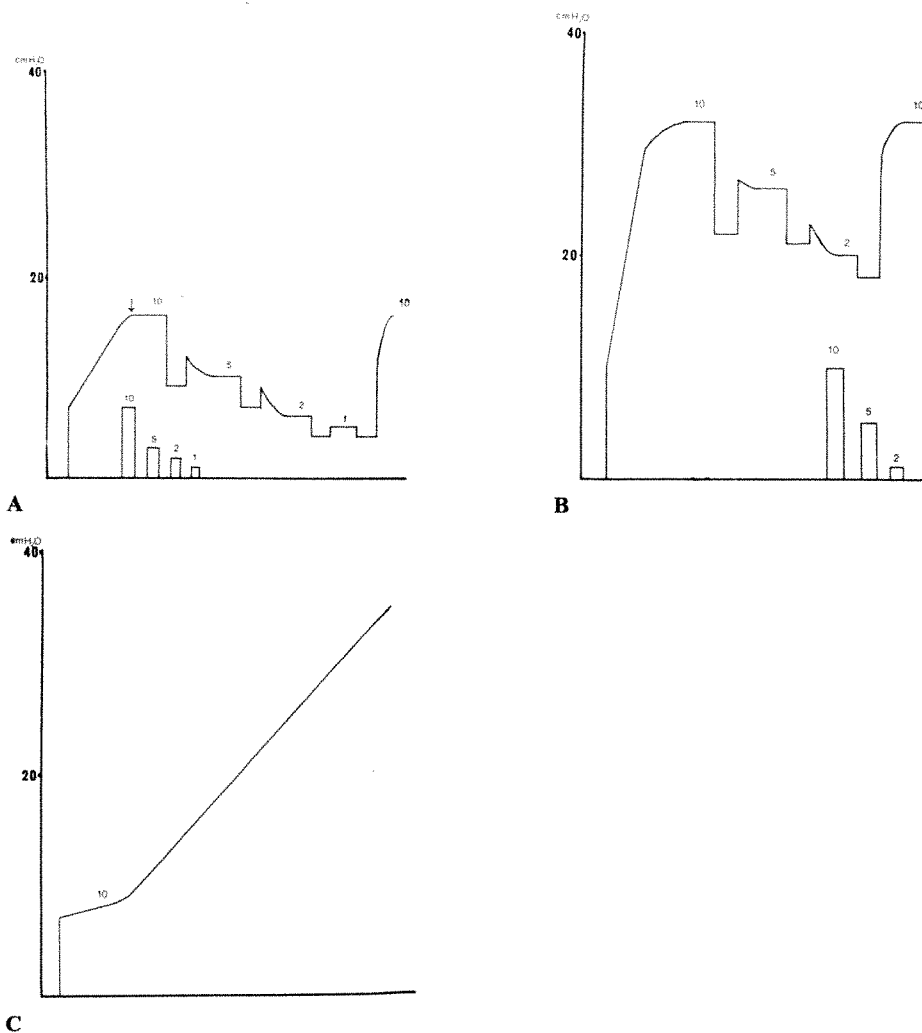


Fig. 4. Three tracings redrawn and simplified. The initial rise in pressure on beginning the perfusion is due to the fixed resistance of the tubing and needle and is reproducible after the study (small tracings in figs. A and B). The small numbers indicate the flow rates. **A**, Normal tracing. The arrow indicates the point at which the pressure becomes constant. **B**, High-pressure tracing. **C**, Obstructed tracing. There is a constant rise in pressure.

maximally filled and the flow rate down the ureter and into the bladder is also 10 ml/min, plus any small contribution from the kidney itself.

This high flow rate is used initially to put maximal stress on the system and in the knowledge that the normal renal pelvis and ureter will tolerate this flow easily with a minimal rise in pressure. Also at this high flow rate the contribution to the total flow which is produced by the kidney, approximately 0.25-0.5 ml/min under the circumstances of this investigation, will be insignificant. If, however, the pressure fails to equilibrate, the flow rate can be lowered to 5 or 2 ml/min to see

if the system will tolerate a lower flow. If the obstruction is complete the pressure will continue to rise whatever the flow rate, and the rate of rise will depend on the flow rate and the degree of dilatation (Fig. 4, c).

The tubing and needle will produce a pressure rise when perfused alone. This rise is determined at each flow rate and subtracted from the final perfusion pressure.

The final pressure within the system can be related to the atmospheric pressure at a point outside the body at the level of the kidney. This is the *absolute pressure* (Fig. 5). By subtracting from this the pressure within the empty bladder, representing the intra-abdominal pressure, a *relative pressure* is obtained, which is in fact the pressure drop across the ureteric orifice. This cancels out the intra-abdominal pressure which is otherwise a variable factor.

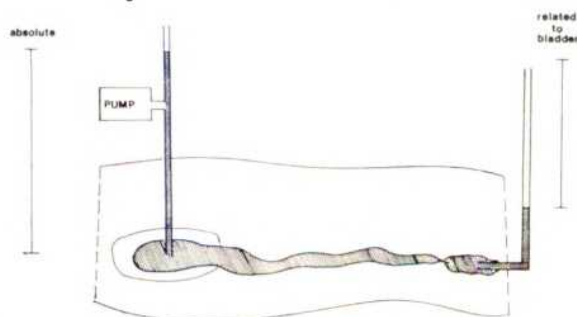


Fig. 5. The *absolute pressure* does not take into account the intra-abdominal or bladder pressures. The *relative pressure* represents the pressure drop from the ureter to the bladder and cancels out the intra-abdominal pressure.

With a nephrostomy tube or percutaneous puncture the fluid used should, at least initially, be a contrast medium so that as perfusion is commenced it is possible to ensure by observing the fluoroscope that there is no leaking around the tubing or puncture site and that the lumen of the tube or needle is lying freely within the pelvis or ureter. Patency of the system is confirmed by a sharp rise in pressure when the patient is asked to cough or the abdomen is pressed.

Valuable information can be obtained by watching the progress of the contrast medium as it fills the renal pelvis and passes down the ureter. Hold-up at the pelvi-ureteric junction or elsewhere in the ureter may be suspected but is only confirmed if there is a concomitant rise in pressure. This observation is modified by whether or not the upper tract is distended with urine before the perfusion begins.

It is important to note whether the medium emerges into the bladder at an initially low pressure or whether a high pressure is necessary before any medium passes through the ureteric orifice (Fig. 6).

Particular note is made of ureteric movement. There may be no intrinsic movement at all, or in a grossly dilated system there may be a rhythmic shake due to the transmitted aortic pulsations. Alternatively, there may be an occasional contraction or even an ineffective peristaltic wave which fails to oppose the ureteric walls and no bolus is pushed on. Often in the dilated lower ureter peristalsis produces a bolus which reaches the lower end and then moves retrogradely back up the ureter for a few centimetres with little fluid entering the bladder each time. Finally, there may be an effective stripping wave which propels a bolus downwards into the bladder.

Apparatus

The studies have been performed at 3 different hospitals with 1 set of apparatus which out of necessity has been kept small, light and portable (Fig. 7).



Fig. 6. Free flow on contrast medium into the bladder from a secondary dilated ureter in a boy with posterior urethral valves. The pressure drop across the ureteric orifice was low, excluding obstruction at this level.

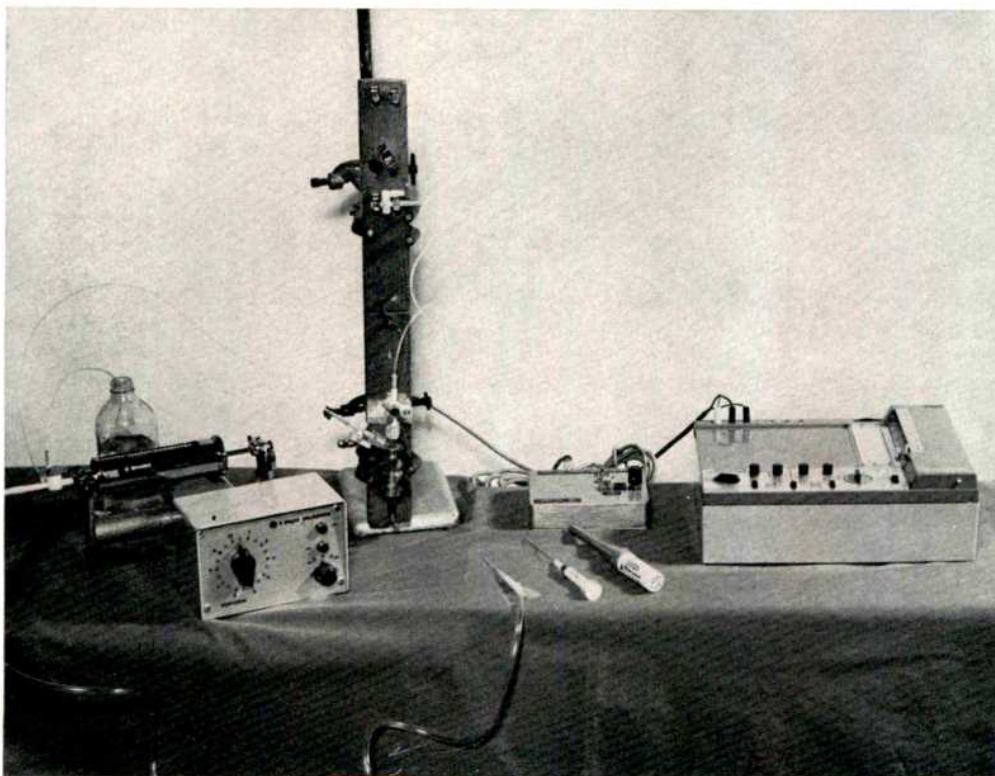


Fig. 7. Perfusion and pressure recording apparatus.

The fluid is delivered from a 50-ml syringe in a "Perfusor" (Braun) constant-infusion pump into a wide-bore Baxter extension tube (BR-34S) which is connected to the nephrostomy tube or needle. A 4-way Baxter stop-cock (BR-62S) allows the pressure to be measured continuously during the perfusion by a Statham P23Db transducer and recorded on a Smiths "Servoscribe M" one-channel recorder. A second stopcock allows intermittent filling of the syringe without removing it from the pump.

All tubing and stopcocks are disposable and only the 50-ml syringe needs autoclaving. The apparatus is calibrated by applying a 20-cm column of water to one arm of the transducer.

Patients Studied

49 studies have been performed in 34 patients whose ages have ranged from 1 month to 65 years. 4 children were under the age of 1 year, 11 between 1 and 6 years, and 9 between 6 and 16 years. The other patients were adults.

Table I shows the methods of access to the upper urinary tracts for perfusion.

Table

Percutaneous antegrade puncture	13
Nephrostomy tube	15
At operation: Lower ureter	15
Upper ureter	2
Renal pelvis	3
Calyx	1
Total number of studies	49

The upper tract dilatation belonged to one of the following 4 categories:

1. **Primary Dilatation.** Here there is an isolated congenital defect at the uretero-vesical junction, unassociated with bladder outflow obstruction. 15 ureters of this type have been studied.
2. **Secondary Dilatation.** Dilatation may be secondary to obstruction to the outflow from the bladder. This is often seen in boys with posterior urethral valves. 7 such ureters were studied.
3. **Post-operative Dilatation.** After ureteric re-implantation there may be persistent or increasing dilatation. There have been 14 such ureters.
4. **Miscellaneous Dilatation.** There is a group of conditions in which obstruction is suspected such as before or after pyeloplasty, in association with a ureterocele, calculus or hydrocalicosis, in retroperitoneal fibrosis or after transuretero-ureterostomy. 13 studies have been performed on examples from this group.

Results

This communication is primarily concerned with a description of the investigation and its usefulness. The full details of the results of all these cases will be presented later.

Amongst the patients studied there were 15 examples of *primary megaureters*. It had been independently decided from the clinical features and radiographic appearances that all these ureters were obstructed in some degree. It was quite clear, however, from the perfusion studies that the group

of *primary megaureters* is not a homogeneous one and that they do not all behave similarly. Some of these ureters tolerated a flow of 10 ml/min with a pressure drop across the ureteric orifice of less than 10 cm water (Fig. 4, A), whilst in others the drop was 20-30 cm water (Fig. 4, B) and in others again the ureter could not tolerate this flow at pressures of less than 100 cm water (Fig. 4, C).

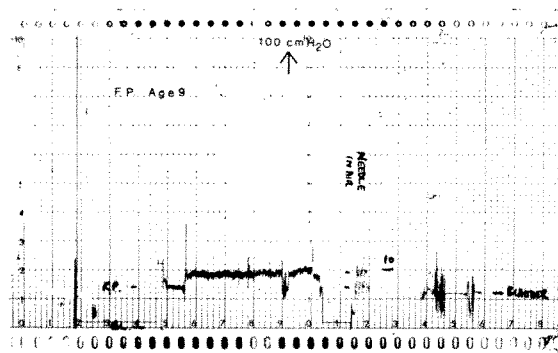


Fig. 8. Tracing of a percutaneous puncture and perfusion in a 9-year-old girl with a dilated ureter after a re-implantation for megaureter. Pressure drop across the ureteric orifice was only 3 cm H₂O at 10 ml/min.

Several ureters in children have remained grossly dilated after re-implantation, but the test has shown that these upper tracts will tolerate 10 ml/min with minimal rises in pressure and on this basis no further surgery has been performed (Fig. 8).

Perfusion of the excised segment of the ureter has correlated poorly with the *in situ* studies, pressures being sometimes greater and sometimes smaller. The dynamic characteristics are inevitably altered during handling and dissection and these *in vitro* studies have now been discontinued.

An example of how useful the test can be is illustrated by a patient with retroperitoneal fibrosis. His upper ureters were perfused before and after ureterolysis and a high residual pressure on one side led to further exploration and lysis. A subsequent pressure determination showed that the ureter would now tolerate a flow of 10 ml/min at a low pressure.

Discussion

It is not surprising that the majority of patients who have been studied by this method are children, as the problem of ureteric obstruction is more common in the younger age-group. However, in several adults with suspected obstruction the test has been of considerable diagnostic value.

All too often during discussions on the management of megaureters, particularly in adults, there are dogmatic statements that either demand that all megaureters should be subjected to surgery or that they should all be left alone. No convincing evidence is offered as to how these rigid treatment regimes are decided upon.

The primary concern in urinary tract dilatation is whether or not a pressure being developed which is sufficiently high to damage the kidney. In addition, the dilatation itself may lead to stasis and a liability to infection. In adults, obstruction is usually progressive and the indications for operative intervention are often clearer. In children, however, it is possible to envisage a situation in which a minor to moderate degree of obstruction exists which is sufficient to cause slow deterioration of renal function perhaps extending over many years. It is in this situation that there is a need for a test which will select the obstructed ureters from those which are just of such poor material that dilatation is inevitable but in which surgery rarely helps and indeed may make matters worse by producing obstruction.

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The standard investigations of intravenous and retrograde pyelography will give some anatomical details but are of little use in assessing degrees of obstruction. Even a nephrostogram will be misleading if it is not pressure controlled as a hand-held syringe can inadvertently produce high pressures. We have found renography of no practical value in the assessment of obstruction in dilated systems.

Perfusion studies of the upper urinary tract are not new (Backlund et al., 1965; Backlund and Reuterskiöld, 1969), but this present method has several advantages. Firstly, as the pressure is measured through the same channel through which the perfusion is introduced there is need for only a single-channel access to the urinary tract. Secondly, by direct puncture above the site of suspected obstruction the system is perfused in such a way that there are no risks of altering the characteristics of the site of obstruction, as is inevitable with the passage of a ureteric catheter. Thirdly, by using a percutaneous puncture and finding a normal pressure on perfusion an exploratory operation can be avoided. Finally, by combining the technique with radiography it is possible to observe and correlate rises in pressure with radiographic evidence of obstruction.

This is a test which involves no complicated urodynamic principles or mathematical formulae. The perfusion is merely a means of simulating a high urine flow to estimate the ability of the upper tract to transport fluid to the bladder. It is designed to give either pre- or inter-operative information concerning the site and degree of obstruction in a practical way which will help the surgeon to decide whether surgery is necessary.

Interpretation of the results is not always easy. A low pressure will certainly indicate that no obstruction is present, and similarly a high pressure will suggest obstruction. However, some pressures have been in the intermediate range and insufficiently few normal systems have been perfused in this way to be absolutely sure of the upper limits of normal pressure at these high flow rates. There are other factors which make the interpretation difficult. Peristalsis will give an uneven tracing from which a representative pressure reading must be taken. Contrast media have a greater viscosity than urine or saline and at a given flow rate will produce a higher pressure. Allowance must be made for this.

Despite these disadvantages, which are all at least to some extent surmountable, this test has proved of considerable value clinically and has helped our understanding of the dynamics and radiological behaviour of the upper urinary tract.

Summary

A simple and informative test is described which will help distinguish the floppy ureter from the obstructed one. The upper tract is perfused at a constant flow rate and the back pressure is measured through a single channel. The procedure is performed under fluoroscopic control and the activity of the ureter is observed.

The test has proved to be of value in both children and adults.

This test was developed at the instigation of Mr D. Innes Williams, who, together with Professor J. P. Blandy, has given encouragement throughout and has supplied the patients for study. Dr A. R. Chrispin, Dr R. S. Murray and Dr T. Sherwood and their colleagues from the X-ray departments of the three hospitals have been generous with their time, help and patience.

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This work was carried out whilst the author was an R.S.O. at the Institute of Urology and The Hospital For Sick Children at Great Ormond Street, London, and the London Hospital.

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An Experimental Model for Evaluating Drug Effects on the Ureter¹

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The literature on the pharmacology of the ureter contains much that is contradictory, and the question "Can the activity of the intact ureter be influenced by drugs?" has not been answered satisfactorily. Greene and Essex (1942) stressed the need to distinguish the effects of changes in urine flow from possible drug effects, and Lapidès (1948) found that alterations in ureteric peristalsis in man, following the administration of a drug, could generally be attributed to a change in urine volume. The demonstration of α and β adrenergic receptors in an *in vitro* pig ureter preparation (Deane, 1967) raised the possibility that mixed stimulation of these receptors could be a further explanation of past confusion. Deane considered that the α receptors were dominant and motor, and the β receptors were recessive and inhibitory. *In vitro* experiments supported this concept (Boyarsky and Labay, 1969) and indicated that noradrenaline infusion stimulated ureteral activity. However, Jackson, Redfern and Ancill (1970) found that noradrenaline decreased the peristaltic activity of the rat ureter and that the β adrenergic receptors mediated the effect of the sympathetic nerve stimulation on the ureter.

This continuing lack of unanimity indicates a need for an experimental preparation giving reproducible results in the hands of different workers.

As it is desirable to be able to repeat the drug experiments on the same subject, the preparation would have to be a laboratory animal which, as far as we are aware, has a ureter with the same properties as that of man, and can be investigated without the need for sedation or anaesthesia. Further requirements would be easy access to the ureter and constant ureteric flow rate and bladder pressure measurements.

The aim of this study was to test an experimental model which fulfilled these requirements.

Materials and Methods

Mongrel female dogs weighing 12-15 kilograms were used.

Under general anaesthesia, the abdomen was opened through a midline incision and an explant pelvicostomy prepared by the following method of Kerr and Peterson (1969). The peritoneum overlying the right kidney was incised, the kidney mobilised and the renal artery and vein divided. The kidney was split and the renal pelvis freed from the parenchyma. The ureter was then mobilised sufficiently to permit the pelvis to be brought through a tunnel in the lateral abdominal wall and sutured to the skin. A small nephrostomy tube was inserted into the left kidney (Struthers, 1963) and the tube led via a subcutaneous tunnel to the animal's neck. If required, an episiotomy was made to facilitate bladder catheterisation. In some animals, a carotid loop was also fashioned.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

Recording Procedure. The animals were trained to lie in a padded trough. The ureter was catheterised by passing a 15 cm length of 4F ureteric catheter through the pelvicostomy, so that the tip lay in the region of the junction of the middle and lower thirds of the ureter. The catheter was connected by polyethylene tubing through a Statham transducer (Fig. 1) to a Harvard constant-rate infusion pump. In later experiments, a polyethylene catheter of similar length, but of smaller external and larger internal diameter than the 4F ureteric catheter, was preferred. The system was filled with normal saline and two perfusion rates, 0.092 and 0.229 ml per minute, were found to

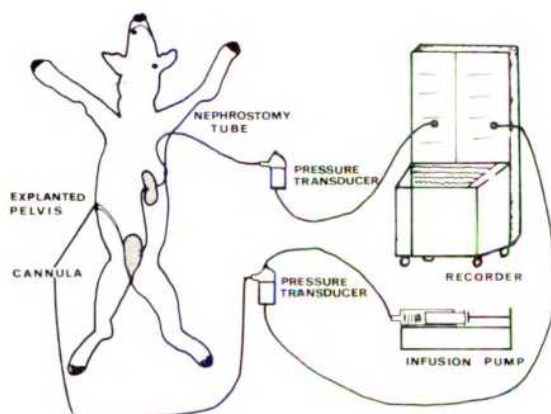


Fig. 1. Diagram of the experimental model: the dog lies in a trough. The catheter in the nephrectomised ureter is infused with saline from a Harvard pump and pressure in the system recorded with a transducer. Pressure is also recorded from the nephrostomy tube in the solitary kidney.

give the most satisfactory amplitude of ureteric wave. At these flow rates, the intrinsic resistance of the system was zero. The nephrostomy tube from the left kidney was also connected to a Statham transducer to monitor pelvic pressures, and arterial pressure was recorded by a cannula from the carotid loop. All pressure tracings were made with a Polygrass pen recorder. The bladder was catheterised and continuously drained. An intravenous infusion of dextrose saline was established, and following a control period of stable recording, the test drug was injected into the intravenous infusion using a Holter pump.

Results

Four dogs were available for study over periods of 2 to 9 months.

Control Perfusion. The ureter was first perfused at 0.092 ml per minute and if the amplitude of the wave was not sufficiently great the higher rate of 0.229 ml per minute was found to be satisfactory (Fig. 2, A and B). The wave frequency was of the order of 2-5 contractions per minute, but the amplitude varied from dog to dog and also in the same dog on different days (Fig. 2, A and C). Bursts of ureteric activity (Fig. 2, D) could be precipitated by moving the ureteric catheter or disturbing the dog with sudden noises, but with the observance of quiet conditions in the laboratory a stable control period was easily established. The use of urine rather than saline as a

perfusate had no effect on the pressure trace, nor did the positioning of the catheter tip in the distal or proximal ureter change the wave pattern.

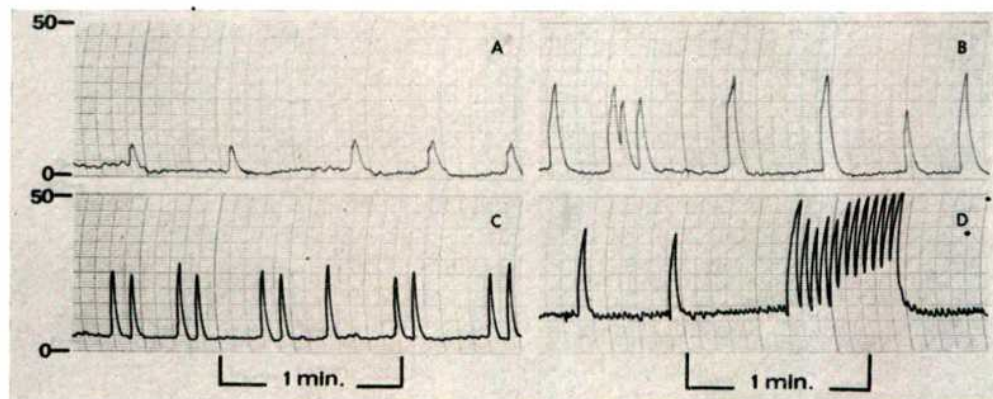


Fig. 2. Contraction waves recorded from the ureter during control perfusion. Pressure is calibrated in centimetres of water. A, at 0.092 ml per minute, and B, at 0.229 ml per minute. C, The same animal at a subsequent experiment showing a higher wave amplitude at the same flow rate as A. D, Burst of ureteric activity produced by a sudden noise.

Drug Effects

(A) **Phenylephrine.** The α adrenergic receptors were stimulated with phenylephrine, 20 μ g per minute, to a total dose of 140 μ g. Within 2 minutes this produced a marked increase in the frequency of ureteric contractions (Fig. 3, A) and a slight rise in pelvic pressure. Urine flow from the solitary kidney was unchanged. The effect on the ureter passed off before the end of the injection. When phentolamine was given to block the α receptors and the ureter again challenged with phenylephrine, no change in ureteric contractions was observed.

(B) **Isoproterenol.** Isoproterenol was given to stimulate the β adrenergic receptors and was infused at a rate of 5 μ g per minute to a total dose of 25 μ g. In spite of the expected changes in blood pressure, no clear-cut effects were observed on the frequency of the ureteric contractions (Fig. 3, B). There was a brief increase in pelvic pressure with contraction waves, and thereafter pelvic waves were absent and the urine flow fell from 8 to 2 ml per minute. Blockade of the α receptors followed by the administration of isoproterenol was also without effect.

(C) **Histamine.** Histamine infusion at 20 μ g per minute to a total of 100 μ g markedly increased the rate of ureteric contraction (Fig. 3, C) and also raised the pelvic pressure and the pelvic contraction rate. Blood pressure was not affected by this dosage.

(D) **Prostaglandin E1.** A transient suppression of ureteric contractions was produced by the administration of 100 μ g of prostaglandin E1 (Fig. 3, D).

(E) **Morphine.** Administration of 2 mg of morphine per minute to dosage of 10 mg had no effect on ureteric contractions (Fig. 3, E).

(F) **Meperidine.** A marked increase of both ureteral and pelvic contractions was obtained with the infusion of meperidine at 10 mg per minute to a total of 50 mg (Fig. 3, F). This response persisted for 5 or more minutes after the end of the injection. Urine flow rate fell from 10 to 2 ml per minute, and there was an increase in the systolic and a fall in the diastolic blood pressure.

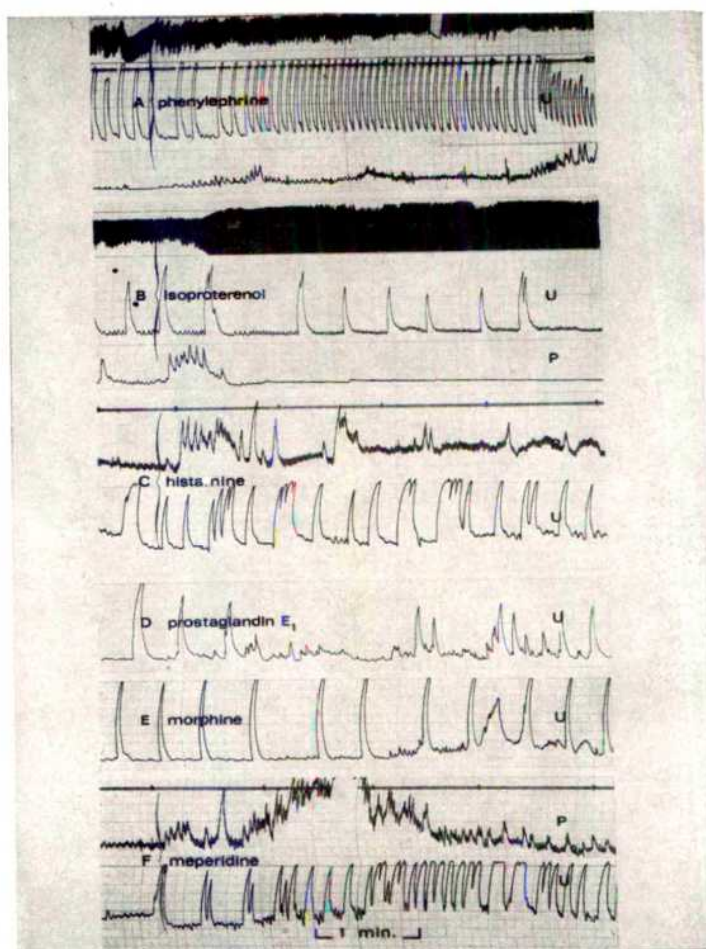


Fig. 3. Response of ureter (U), renal pelvis (P) and blood pressure (BP) to intravenous drug infusion. A, 140 μ g phenylephrine. B, 25 μ g isoproterenol. C, 100 μ g histamine. D, 100 μ g prostaglandin E₁. E, 10 mg morphine. F, 50 mg meperidine.

Discussion

The explanted pelvicosomy preparation provided access to the ureter without the disadvantages found with the bladder explant technique (Boyarsky and Labay, 1972) and the use of perfusion assured a constant ureteric flow rate with the production of a fairly regular pattern of contraction waves. When used frequently, the pelvicosomy remained open and there was no change in the character of the ureteric waves during a 9-month period of observation. Thus, repeated evaluation of drugs could be made and any response distinguished from the effects of spontaneous variations in rhythm. The problems of analysis of ureteric pressure tracings have been discussed by Boyarsky and Labay (1972) and a complicated method of evaluation using the distribution of peristaltic intervals has been described by Dale, Constantinou, Briggs and Govan (1971). Fortunately, with this experimental model, the increase in frequency of peristalsis produced by phenylephrine,

histamine and meperidine was clearly apparent; however, Kiil and Kjekshus (1967) have warned that a change in rate of ureteric peristalsis must not be equated with a change in the power of ureteral contractility. As drug effects have been reproducible, the model offers possibilities for the development of drugs with specific effects on the ureter and ultimately the pharmacological manipulation of ureteric peristalsis in man.

Summary

An explanted renal pelvis preparation in the dog is described. This experimental model permits ureteric catheterisation in the conscious animal and the recording of ureteric contraction waves under controlled conditions.

Studies with this model have shown that the frequency of peristaltic contractions in the intact dog ureter can be influenced by pharmacological means, and suggest that this technique may be used for the screening of drugs for their effects on ureteric activity.

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Urinary Fistulae after Renal Transplantation¹

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Urinary fistula following renal transplantation is a potentially serious complication (Williams, 1970; Rees, 1972). The mortality rate in reported series has varied from 25 to 50 per cent (Palmer *et al.*, 1969; Starzl *et al.*, 1970; Robson and Calne, 1971).

This paper presents our experience with urinary fistulae in a consecutive series of 130 renal transplants from February 1961 to March 1972.

Table

Urinary Fistulae after Renal Transplantation

No.	Patient	Fistula	Donor	Day of Onset	Treatment	Result
1	K. B.	Vesical	Living	17	Bladder drainage	Died of sepsis
2	W. M.	Vesical	Cadaver	15	Bladder drainage	Satisfactory
3	P. C.	Vesical	Cadaver	13	Bladder drainage	Satisfactory
4	J. B.	Vesical	Cadaver	14	Bladder drainage	Satisfactory
5	B. B.	Vesical	Cadaver	22	Bladder drainage	Satisfactory
6*	G. R.	Vesical	Cadaver	12	Bladder drainage	Died of unrelated causes
7	J. W.	Vesical	Living	11	Bladder drainage: immunosuppression stopped	Satisfactory
8	M. H.	Vesical	Cadaver	16	Bladder drainage	Satisfactory
9	D. O.	Vesical	Cadaver	18	Bladder drainage	Satisfactory
10	N. M.	Ureteric	Living	1	T-tube intubation	Died of sepsis
11	J. L.	Ureteric	Cadaver	14	Ureteric re-implantation	Transplant nephrectomy
12	N. F.	Ureteric	Living	3	Uretero-ileostomy	Satisfactory
13†	J. H.	Ureteric	Cadaver	4	Uretero-ileostomy: immunosuppression stopped:	Satisfactory
		Calyceal		74	omentopexy	
14	M. S.	Calyceal	Cadaver	27	Uretero-ureterostomy: immunosuppression stopped: omentopexy	Satisfactory
15	E. O'N.	Calyceal	Living	24	Omentopexy: ureteric stricture excised: ureteric re-implantation	Satisfactory

* Excluded from mortality rate assessment because of early death from unrelated causes.

† This patient had 2 fistulae.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

have followed injury of the ureter at nephrectomy (patient 10); 1 followed primary detachment of the ureter and was associated with secondary haemorrhage (patient 11); 2 followed ureteric re-implantation for ureteric obstruction (patients 12 and 13). Histological examination failed to reveal any evidence of rejection in the ureters. One of the 4 patients died and 1 required transplant nephrectomy. The remaining 2 are well 4 and 6 years later with functioning transplants.

Patient 10 (N. M.). Excessive urine leak on the 1st postoperative day led to early exploration when a juxta-vesical ureteric fistula was found and drained by a ureteric T-tube. The fistula persisted, septicaemia and secondary haemorrhage developed and the patient died on the 27th postoperative day.

Patient 11 (J. L.). When exploration was required on the 14th day after transplantation for secondary haemorrhage from the arterial anastomosis, the ureter was found detached from the bladder. Subsequent haemorrhage necessitated transplant nephrectomy but the patient eventually received a second kidney and has remained well for 3 years.

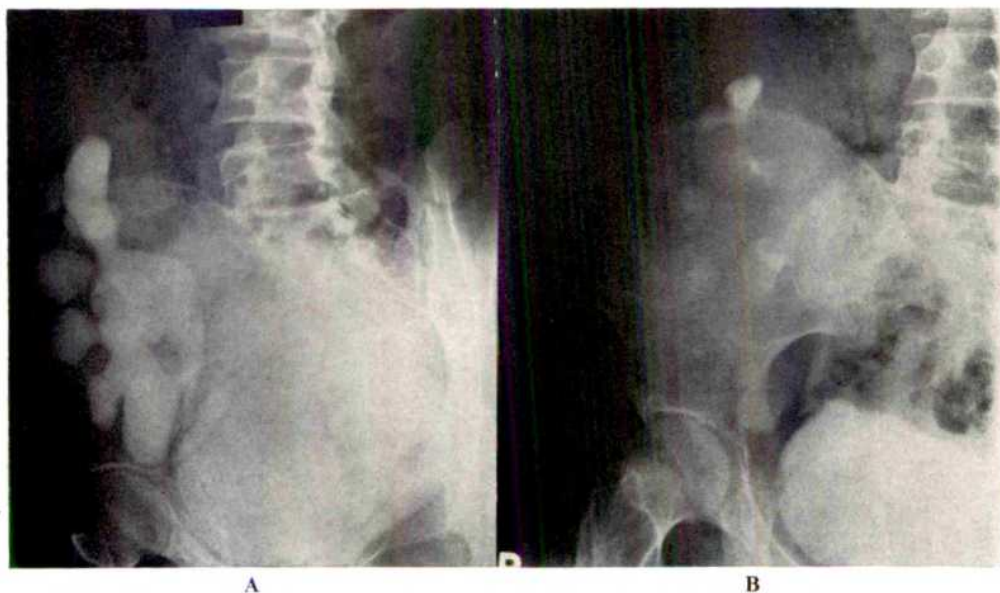


Fig. 2. Patient 12 (N. F.). (A) Calyceal dilatation 4 years after uretero-ileo-cystoplasty. (B) I.V.P. after excision of ileal segment and re-implantation of ureter into bladder.

Patient 12 (N. F.). Recurrent ureteric obstruction required two separate attempts at ureteric re-implantation on the 5th and the 21st post-transplant days. A splint was used for the second operation but failed to prevent a juxta-vesical ureteric fistula. A further attempt was made to deal with this by T-tube ureteric intubation, but the urine leak persisted and on the 39th post-transplant day a temporary uretero-ileostomy was carried out: this cured the leak and 4 months later the uretero-ileostomy was converted to a uretero-ileo-cystoplasty. Four years later there was pyelographic evidence of increasing calyceal dilatation with distal ureteric obstruction and this was cured by mobilising the bladder and re-implanting the ureteric remnant after excision of the ileal loop (Fig. 2).

Patient 13 (J. H.). Following ureteric re-implantation and T-tube intubation for recurrent ureteric obstruction, the distal portion of the ureter was found to be necrosed and a temporary uretero-ileostomy was required. Twenty-three months later uretero-ileo-cystoplasty was carried out and normal micturition restored. Although azathioprine was discontinued for 8 months renal function did not decline, the creatinine clearance remained unchanged and the patient remains well 4 years after transplantation.

Calyceal Fistulae. Three patients developed calyceal fistulae. In 2 the cause was ligation of polar vessels but in the remaining case the cause of the fistula was obscure. The urine leaks occurred

between the 24th and 72nd post-transplantation days. All are well with satisfactory renal function 2, 4 and 5 years after transplantation.

Patient 13 (J. H.). The ureteric fistula in this patient has been described. Following uretero-ileostomy there was still some leak of urine and on re-exploration there was necrosis of the lower pole of the kidney. The sloughing parenchyma was removed, the calyx sutured and a free muscle graft applied. But not until 2 months later when a pedicle omental graft was used as in case 14 was the fistula finally cured.

Patient 14 (M. S.). The calyceal fistula in this case recurred after an initial attempt had been made to close it by suture and application of a free muscle graft. Uretero-pyelography through a catheter in the fistula suggested obstruction in the juxta-vesical part of the ureter and uretero-ureterostomy, using the ipsilateral ureter of the recipient (Fig. 3) and a pedicle omental graft, was required to cure the condition. As in case 13, azathioprine was discontinued for several months and the patient remains well with good renal function 4 years after transplantation.

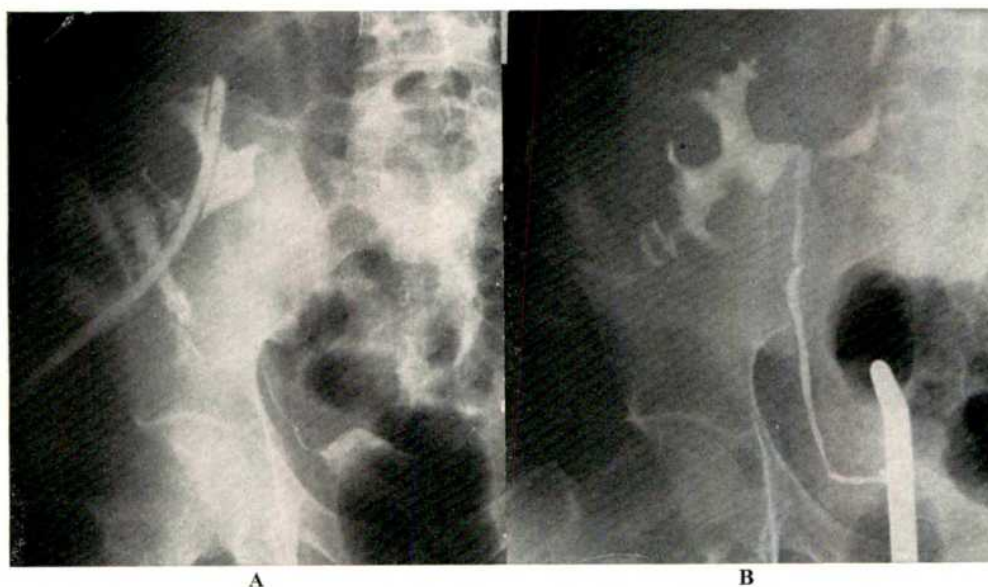


Fig. 3. Patient 14 (M. S.). (A) Ureteropyelogram through calyceal fistula. (B) Side-to-side uretero-ureterostomy: the calyceal fistulous track can also be seen.

Patient 15 (E. O'N.). A urine leak 24 days after kidney transplantation was found to be due to a circular necrotic zone in the front of the kidney involving the middle calyx. An omental pedicle graft was wrapped around the kidney, but a urine leak persisted until a juxta-vesical ureteric stricture was excised and the ureter re-implanted into the bladder. Histological examination of the renal cortex and the ureter failed to show any evidence of rejection.

Discussion

It is not always easy to determine the site of origin of a urinary leak after transplantation. Provided that the indwelling urethral catheter is not obstructed, a urinary fistula which develops within 3 days of kidney transplantation should be explored as an urgent procedure. A urine leak may be minimal and be overlooked when a transplanted kidney is oliguric, for example when there is acute tubular necrosis or severe rejection. Retrograde cystography may be valuable but intravenous pyelograms, radioisotope scans and the use of dyes have been particularly helpful (Rees, 1972). Retrograde uretero-pyelography is sometimes possible (Robson and Calne, 1971).

A vesical fistula should close spontaneously after continuous bladder drainage, but if the leak persists, a more proximal fistula should be suspected. The management of a ureteric fistula is

more difficult and there is a significant incidence of complications following re-implantation of the ureter. The use of ileal segments in patients 12 and 13 was influenced by the fact that vesico-ureteric reflux was present in 1 and a nephro-ureterectomy had been carried out previously in the other; in any case there is a high incidence of complications following uretero-ureterostomy and ureteropyelostomy (Ekman *et al.*, 1968; Starzl *et al.*, 1970; Weil *et al.*, 1971). A Boari flap or a psoas hitch operation with direct anastomosis of the renal pelvis to the bladder may be possible (Rees, 1972) and a pedicle omental graft may also be of value (MacKinnon *et al.*, 1968). Our results with ureteric intubation have been unsatisfactory and the tubes may have been responsible for the development of pressure necrosis in 2 cases and obstruction of the tube by debris occurred in 1 other.

Calyceal fistulae characteristically occurred after an interval of at least 3 weeks from transplantation. The mechanism in 2 patients was ligation of a polar vessel, but in the third the local necrotic zone involving a middle calyx was unexplained. It has been postulated that this may be due either to embolism from the arterial suture line or to local vasospasm (Fox and Tottenham, 1972). Provided that distal ureteric obstruction has been excluded, the necrotic tissue should be excised where possible, and that area of the kidney covered by a pedicle omental graft. A temporary nephrostomy for either calyceal or other urinary fistulae has been needed only rarely in our experience.

Routine prophylactic antibiotic cover has been avoided because it is felt that superadded infection with resistant organisms is a particular hazard in immunosuppressed patients. However, when there is an unexplained fever and the diagnosis remains obscure, "blind" antibiotic therapy may be justified. It is sometimes better to stop the immunosuppressive therapy when it is felt that it is responsible for delayed wound healing or when there is a risk of spreading infection. The kidney is not necessarily rejected when this is done and, indeed, this was the case in patients 7, 13 and 14 who continued with good function of the transplants despite withdrawal of azathioprine for periods from 1½ to 8 months.

Summary

In 130 consecutive patients treated by renal transplantation in the years 1961 to 1972 there were 9 patients who developed a vesical fistula, 4 developed a ureteric fistula and 3 a calyceal fistula (1 patient had both a ureteric and calyceal fistula).

Continuous bladder drainage by an indwelling urethral catheter is recommended for the treatment of a vesical fistula.

The treatment of a ureteric fistula may be difficult and a temporary uretero-ileostomy may be of value.

Provided that distal obstruction is excluded, omentopexy is valuable for treating a calyceal fistula.

Immunosuppressive drug therapy may have to be withdrawn but this is not always followed by rejection of the transplanted kidney.

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Vesico-intestinal Fistulae and Recto-urethral Fistulae¹

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Fistulae between the urinary and alimentary tract are rare. Those seen in our patients can be classified into three groups:

I. Vesico-intestinal fistulae	9
II. Uretero-intestinal fistulae	2
III. Urethro-rectal fistulae	12
	—
Total	23

Urinary intestinal fistulae can also be classified in the following way: congenital, inflammatory, traumatic and neoplastic. Congenital fistulae usually occur together with other anomalies, such as imperforate anus. Vesico-intestinal fistulae appear most often as a result of an inflammatory process, such as diverticulitis, Meckel's diverticulitis, appendicitis, Crohn's disease, and in tuberculous lesions. Traumatic fistulae are caused by war or accidental injuries, as well as a complication following surgery—prostatectomy and transurethral resection of the prostate. There are on record individuals developing a vesico-rectal or urethro-rectal fistula caused by a fall on a sharp-edged rail, fence or wire. Neoplastic fistulae develop due to necrosis of a tumour of the bladder, sigmoid colon or rectum. An accurate and thorough knowledge of the character of the disorder and its relation to the resulting injury will greatly facilitate diagnosis.

The early symptoms are usually associated with disorders of the alimentary tract, which are followed by frequency, haematuria, pneumaturia and dysuria. During micturition gas and small particles of faecal material pass through the urethra. Urine may leak through the rectum during defaecation. One of our patients told us in the interview that she noticed poppy seeds in her urine after eating poppy-seed cake. This symptom suggested the existence of a vesico-intestinal fistula. Since then we have successfully applied this poppy-seed test in other patients suspected of having vesico-intestinal fistulae.

Radiological investigation of the urinary and alimentary tract is the essential examination in making a diagnosis. During cystography injected dye may leak to the bowel through a fistula. Similarly, during investigation of the alimentary tract, the dye may penetrate from the intestine to the bladder. Cystoscopy reveals an inflammatory or a neoplastic lesion in the region of the fistula, and in some cases it is possible to observe the orifice of the fistula. A biopsy should be taken for histopathology and it may be possible to insert a ureteral catheter through the fistula into the bowel. The dye injected through the catheter enables identification of the intestinal segment.

Treatment of vesico-intestinal fistulae is generally a surgical procedure. Depending upon the type and size of the fistula and the general condition of the patient, surgery may be carried out in one or two stages. In the case of vesico-intestinal fistulae the place of the fistula should be found and all fistulous tracks into the neighbouring tissues, including part of the bladder and the segment of the intestine, must be resected. Next, intestinal anastomosis and suture of the bladder must be

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done. Diversion of the urine is provided by cystostomy. In the case of vesico-colonic fistulae it may be wiser to perform a transverse colostomy as a first stage, and next, after some time, partial resection of the colon and bladder. In the case of a neoplastic fistula, as a rule a multi-stage procedure is recommended.

Case 1. A male, aged 29, presented with painful frequency, pyuria, *E. coli* infection, pneumaturia and faecaluria. After consuming a cake with poppy seed, he noticed its seeds in the urine. Cystoscopy showed the opening of the fistula above the right ureteric orifice. During cystography the dye penetrated into the bowel (Fig. 1). Barium enema showed the appendix filled with barium and connected via a fistula to the bladder (Fig. 2). A laparotomy was done. The end of the appendix was adherent to the bladder wall. Appendicectomy and partial resection of the bladder and closure of the bladder with an indwelling catheter was done. Fifteen days later he left hospital and was well. Follow-up cystoscopy some months later did not show any fistula and the patient passed urine without trouble. There was no urinary infection. It is worth noting that his bladder disorder had lasted for 10 years since the first symptom of acute appendicitis.

Among our patients we had 9 with vesico-intestinal fistulae: inflammatory, 4 cases (3 cases post-appendicitis, 1 case post-operative pelvic abscess); traumatic, 1 case (1 gunshot wound of the abdomen) and 4 neoplastic cases caused by adenocarcinoma of the sigmoid colon. Patients with inflammatory and traumatic vesico-intestinal fistulae, 5 cases, healed after treatment. Patients with neoplastic fistulae developed recurrence of the tumour in a short time.

Uretero-intestinal fistulae after gynaecological operations are very rare. From December 1949 to February 1972 inclusive we treated 135 women with 167 ureteral injuries caused during gynaecological or obstetrical operations. Among these patients we observed only two cases with uretero-intestinal fistulae.

Case 2. A female, aged 36, presented with leakage of urine through the vagina, pain in the right lumbar region, and pyrexia. Some weeks earlier subtotal hysterectomy was performed for fibroids, and during the operation the right ureter was transected and sutured, and a right nephrostomy was done. A fortnight later the catheter slipped out, the nephrostomy closed immediately and, to our amazement, the patient did not suffer from any vaginal urinary leakage. Uretero-pyelography showed penetration of the dye from the ureter to the ileum. The patient was content with being dry and would not agree to another operation.

Case 3. A female, aged 40, while crossing a fence, got stuck on a sharp-edged rail and had her vagina, uterus and rectum damaged. An emergency operation was necessary: the uterus was removed and the vagina and rectum repaired. During the gynaecological operation both ureters were damaged. Three days later bilateral nephrostomy was performed, and a colostomy was done after a month. One year later the patient presented at our clinic with a right uretero-vaginal fistula, a left nephrostomy, a colostomy and a vagino-rectal fistula. During our operation for bilateral ureteral re-implantation, a left uretero-sigmoid fistula was found. After this operation the right side healed but the left uretero-vaginal fistula persisted, and only after further re-implantation of the ureter was the fistula cured.

We observed 12 cases of urethro-rectal fistulae—congenital, 6 cases after operation for imperforate anus; 6 traumatic cases; 2 cases of gunshot wound; 3 cases of accident during work and 1 case after transurethral resection of the bladder neck. One patient from this group refused operation, whilst the remaining 11 were all repaired by the Whitehead-Young-Stone procedure; 2 cases were operated on twice. In another two cases the result was poor; urethro-rectal fistula persisted. We consider the Whitehead-Young-Stone method to be one of the most effective procedures. It is my patriotic duty to mention the operation developed by Ziembicki, who was the first to introduce the principle of freeing and rotating the rectum in order to avoid the opposition of the two suture lines after closing the urethra and rectum. He presented a patient cured by this method to the Society of Medicine in Lemberg on 30th March 1889. Young and Stone described his ingenious method in 1913 and 1917. This procedure has produced excellent results in our patients. Couvelaire and Cukier described nine cases of urethro-rectal fistulae repaired mostly by a coccygo-perineal procedure. Readers interested in the operative procedures may refer to the highly instructive paper by Weyrauch (1951), who presents the historical development of surgical treatment of urethro-rectal fistulae.

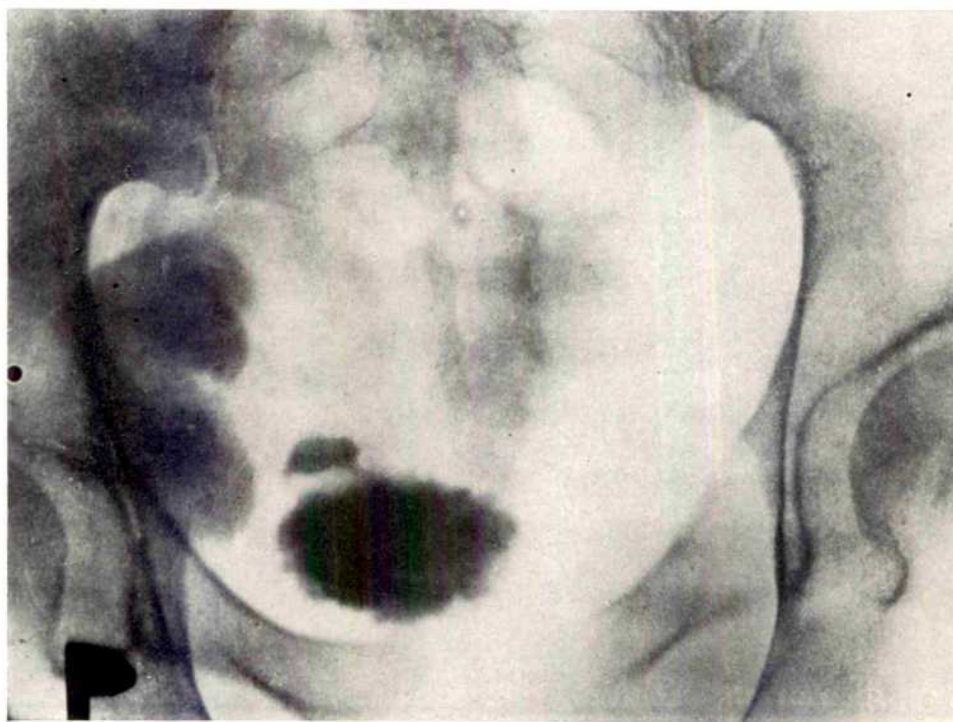


Fig. 1. Case 1. Cystography—the dye penetrates from the bladder into the bowel.

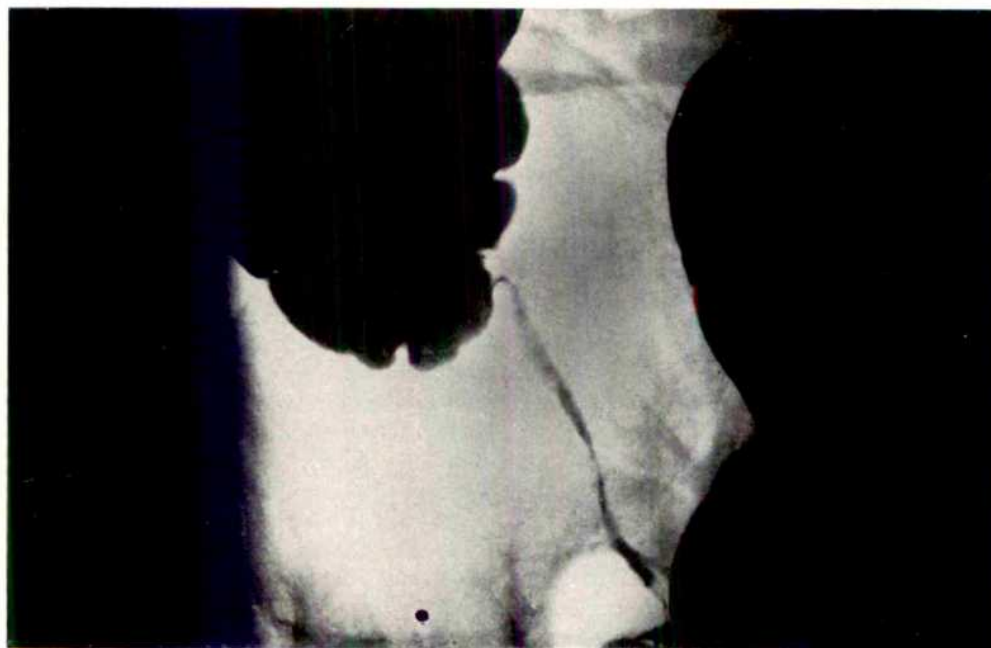


Fig. 2. Case 1. Appendico-vesical fistula. During enema barium penetrates through appendix into the bladder.

Case 4. A male, aged 20, in childhood operated on for imperforate anus. Since that time he had a persistent urethro-rectal fistula. On 10th November 1970 the Whitehead-Young-Stone operation was done. A circular incision around the anal orifice and dissection of the rectum above the fistula was carried through the dilated anal sphincter. The fistulous rectal opening was brought down to the skin level and the dissected segment of rectum resected together with the fistula. Next, the edges of the urethral fistula were excised and the fistula was closed transversely with interrupted catgut sutures. The rectal mucosa was sutured to the skin. An indwelling Foley catheter was left in position for 2 weeks. The postoperative course was uneventful. After removing the catheter the boy passed urine perfectly. Follow-up examination 18 months postoperatively showed an excellent result.



Fig. 3. Case 5. Urethro-cystography. Urethro-rectal fistula.

Case 5. A male, aged 22, with a urethro-rectal fistula (Fig. 3) after operation for imperforate anus four times. In childhood he suffered from poliomyelitis. On 17th June 1971 a Whitehead-Young-Stone operation was done, with a cystostomy. The postoperative course was difficult due to very severe bladder spasms. The boy was in a highly nervous condition and there was absolute lack of co-operation. The result was poor and the urethro-rectal fistula persisted. Six months later he presented at our clinic for a check examination and refused another operation, saying that he felt very satisfied as he now passed all his urine smoothly through the rectum while previously urine passed both through the rectum and urethra, which was far less convenient.

It must be once more emphasised that the Whitehead-Young-Stone operation is an excellent procedure in these cases. Two of our cases with poor results had previously had multiple operative procedures, and 1 showed complete lack of co-operation in the postoperative period.

Summary

23 cases of urinary intestinal fistulae are presented: vesico-intestinal fistulae, 9 cases; uretero-intestinal fistulae, 2 cases; urethro-rectal fistulae, 12 cases. Out of the 11 operations for urethro-rectal fistulae, 2 were unsuccessful. All the urethro-rectal fistulae were repaired by the Whitehead-Young-Stone method, which the author recommends.

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The Types of Neuropathic Bladder Dysfunction associated with Prolapsed Lumbar Intervertebral Discs¹

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Clinically, it has long been recognised that prolapse of lumbar intervertebral discs can cause disturbances of bladder function. Sometimes this is associated with the classical symptoms and signs in the back and lower limbs of peripheral nerve root involvement. More recently a number of cases has been reported in which bladder dysfunction has been the sole or primary manifestation.

During the last 2½ years, in the course of investigating many cases of neuropathic bladder dysfunction referred to the Department of Urology at the Manchester Royal Infirmary, 5 cases presenting primarily with bladder symptoms due to central prolapse of lumbar intervertebral discs have been encountered. This series demonstrates a wider range of bladder disturbance due to this lesion than has previously been described.

Case 1. T. A., a 54-year-old male, was referred to a surgical unit complaining of marked daytime frequency and nocturia for several months. Clinically he was thought to have moderate prostatic enlargement. The urine was normal and I.V.P. showed normal upper tracts, a trabeculated bladder and a small amount of residual urine. On admission some months later he complained of severe diurnal frequency, urge incontinence, mild intermittent low back pain and numbness in the left thigh. He was referred to the urological department. On examination we thought that the prostate was not significantly abnormal, and the bladder was not palpable. There was loss of lumbar lordosis, scoliosis convex to the left, and limitation of flexion and S.L.R. by back pain. There were no signs in the lower limbs of saddle area. M.S.U. and blood urea were normal. At cystoscopy there was 80 ml of "residual" urine, moderate trabeculation and a small basal diverticulum. The bladder neck, prostate and urethra were normal. Cystometry (Fig. 1) revealed 60 ml residual urine, normal sensation and a severely uninhibited bladder with uncontrolled voiding around the Gibbon catheter at 90 ml filling. Lumbar myelography (Figs. 2 and 3) showed indentation of the myeloid column opposite the L4/5 and L5/S1 disc spaces. A neurosurgical opinion was sought. The spine was explored. A large central prolapse of the L4/5 disc and a smaller prolapse of the L5/S1 disc were found and both discs were excised. On the 4th day after operation the patient voided normally and with full control. He was discharged home without symptoms on the 14th day. At follow-up 2 months later he had mild urgency but considered his symptoms to be vastly improved. Repeat cystometry (Fig. 4) showed the first desire to void at 170 ml and this was followed by rapid emptying. Eighteen months after operation, he had no back symptoms, frequency or incontinence, but still had a mild degree of urgency.

Case 2. W. Q., a 32-year-old male, presented with frequency, urgency, enuresis, low back pain and a feeling of heaviness in the legs, of 9 months' duration. Clinical examination was normal, apart from bilateral pes cavus, brisk lower limb reflexes and an equivocal left plantar response. Sensation in the saddle area and anal tone were normal. M.S.U., urea and I.V.P. were also normal. Cystometry revealed no residual urine, intact sensation, and an uninhibited bladder with reflex emptying around the catheter. Capacity was 200 ml. Myelograms showed no definite disc lesion, but it was suggested that the conus medullaris might be slightly expanded. The spine was explored and a large central disc prolapse at the L5/S1 level was found and removed. The conus looked normal. After operation his bladder and back symptoms rapidly improved. He was discharged from hospital at 14 days. He has since returned to his native Eire and we have not seen him for follow up.

Case 3. C. B., a 25-year-old male, presented with a 10-month history of frequency and urge incontinence. Four years previously a disc lesion was removed for severe back pain and sciatica. Later these symptoms recurred and

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

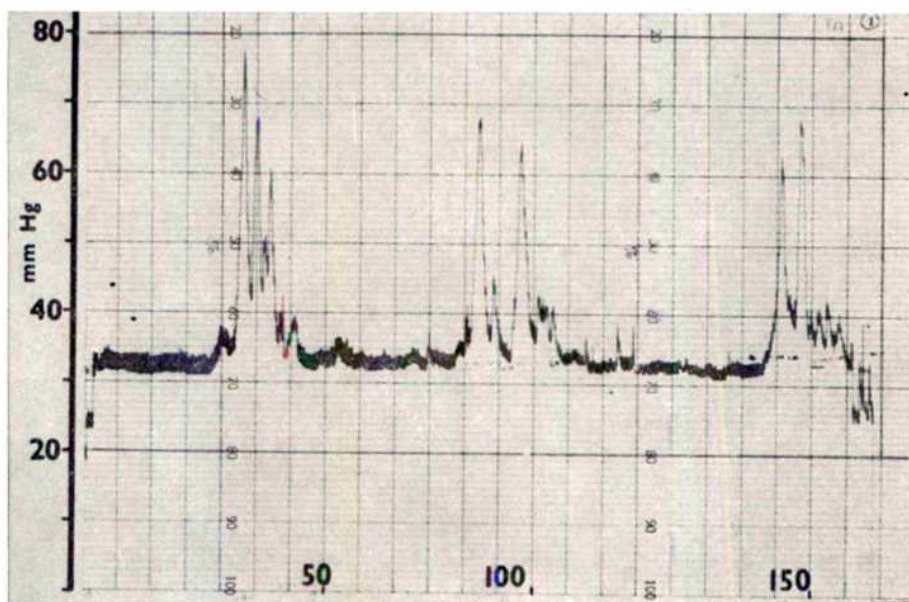


Fig. 1. Case 1. Cystometrogram prior to operation.

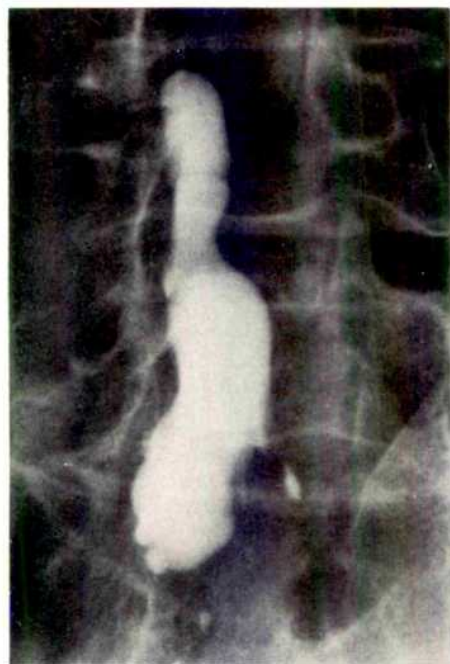


Fig. 2. Case 1. Lumbar myelogram, oblique view.

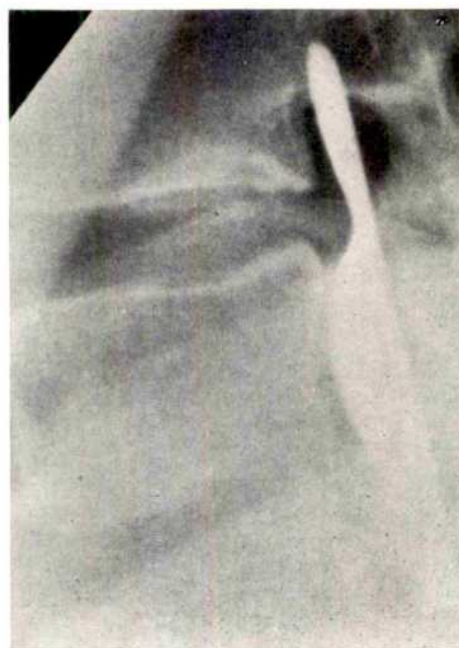


Fig. 3. Case 1. Lumbar myelogram, lateral view.

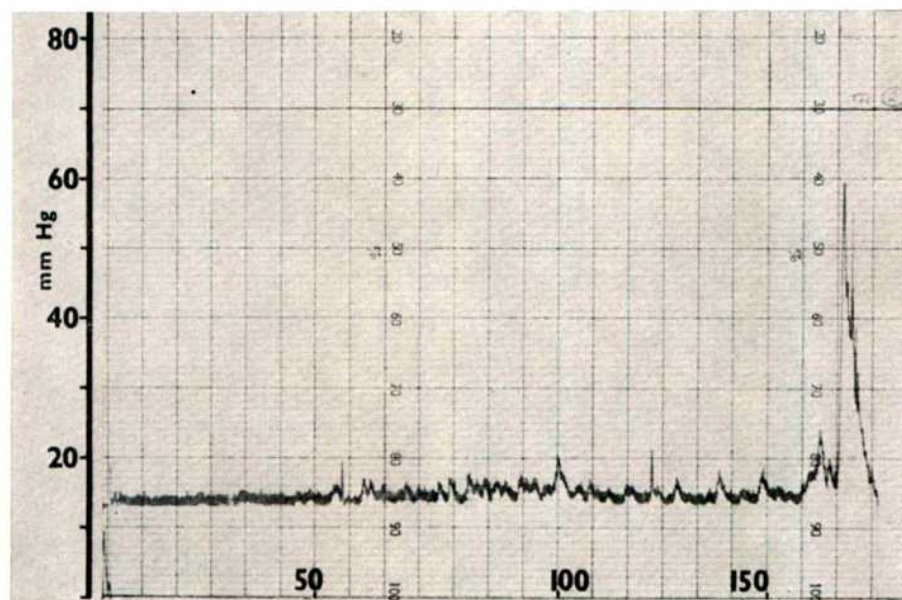


Fig. 4. Case 1. Cystometrograph 2 months after operation.

simultaneously his urinary symptoms began. By the time that he was referred for a urological opinion, he was beginning to complain also of difficulty in maintaining his urine flow. The positive clinical findings were restriction of lumbar spine movements and S.L.R. The left knee and ankle jerks were depressed and sensation was diminished in the left posterior thigh and saddle areas. M.S.U., urea and I.V.P. were normal. At cystometry there was no residual urine, sensation was normal and uninhibited detrusor contractions occurred from the early stages of filling, with uncontrolled voiding at 150 cc. Myelograms were normal. The spine was explored and a large central prolapse of the L5/S1 disc was found and removed. Two weeks later micturition was normal and his back pain and sciatica had gone. Six months after operation he was asymptomatic. At one year he complained of mild urgency when under stress. Repeat cystometry at this time revealed normal bladder function.

Case 4. A. H., a 61-year-old female, presented with an 18-month history of frequency and urgency. She had also complained of severe R.I.F. and flank pain for 5 years. Orthopaedic consultations and a laparotomy had failed to reveal any cause for this. Clinical examination showed no significant abnormality. M.S.U., blood urea and I.V.P. were normal. At cystoscopy, residual urine was 40 ml. The bladder was trabeculated with a shallow diverticulum on the left side. Cystometry showed that sensation was normal and uninhibited contractions resulted in voiding around the catheter at 110 ml. Myelograms revealed indentations at L3/4, L4/5 and L5/S1 levels. Disc protrusions were confirmed and removed at all three levels at operation.

Postoperatively the patient was free from pain and micturition was normal after the first few days.

Case 5. F. A., a 64-year-old female, was referred to the Urology Department from the Eye Hospital where she had been admitted for a cataract operation and found to have a painless bladder distension. She had previously complained, for some months, of urgency, nocturia, enuresis and dribbling incontinence. Blood urea was 78 mg per cent, the urine infected with *E. coli*, and I.V.P. showed bilateral upper tract dilatation. W.R., blood sugar and glucose tolerance tests were normal. There were no positive C.N.S. findings. Cystoscopy revealed a residual urine of 600 ml, bladder capacity was over 800 ml and there was inflammation and trabeculation. Myelograms showed disc protrusions at L4/5 and L5/S1. At operation central prolapses were found at both levels and the discs exenterated. Her bladder function improved slowly over the following weeks. Three weeks after operation the residual urine was 250 ml, and bladder sensation was returning. She was discharged home 5 weeks after operation with no significant residual urine and normal voiding. One year after operation she remains asymptomatic.

It will readily be seen that 4 of our 5 cases presented with irritative bladder symptoms without appreciable loss of bladder sensation, and that cystometry showed an uninhibited type of neuro-pathic bladder dysfunction with low residual urine and a decreased functional capacity. The third

patient, though complaining initially of gross irritative symptoms was, at the time of presentation, beginning to experience difficulty in maintaining urine flow. The fifth patient, though presenting with a chronic painless retention, gave a preceding history of urgency, nocturia and enuresis.

Myelography was positive in 3 of the 5 cases, negative in 1 and misleading in the remaining case. All our cases had a central prolapse of 1 or more lumbar discs between the L3/4 and L5/S1 levels.

In 1965, Malloch reported 3 cases of *acute* retention occurring in patients with classical signs and symptoms of disc protrusion of 1 to 4 days' duration. Each had a massive central disc prolapse removed as an emergency procedure, but recovery of normal bladder function in these cases was slow.

Yaxley (1966) presented a similar case in which recovery of bladder function only began 14 months after operation and was complete at 2 years.

Emmett and Love (1967 and 1968) first described 3 cases of chronic urinary retention in women, associated with otherwise asymptomatic lumbar disc prolapse. All recovered rapidly after removal of the discs.

Ross and Jameson (1971) reported their experience with 40 cases of bladder dysfunction due to disc prolapse, though only 9 of their cases were of the "occult" type presenting primarily with bladder dysfunction and responding to operative treatment. They pointed out that single nerve root lesions are unlikely to cause bladder dysfunction, but a massive central prolapse or multiple-disc lesions are more likely to cause disturbances of voiding. They concluded that the first evidence of bladder dysfunction is impaired bladder sensation and that large central lumbar disc protrusions are likely to lead to a lower motor neurone type of bladder affection.

Emmett and Love (1971) extended their series to 35 cases and reported various types of bladder dysfunction due to prolapsed lumbar discs. They concluded that the problem involves more than just total urinary retention, that both sexes may be affected and that bladder disturbance may be encountered in patients who also have typical disc symptoms. Our own findings confirm this. Only 40 per cent of their cases had positive myelograms and they found that the most useful aid to diagnosis was cystoscopy without anaesthesia. Typical findings were reduced bladder sensation, lack of desire to void, absence of trabeculation, increased capacity and normal expulsive force through the instrument.

Cystometry has the added value of producing a permanent record and objective measurements of detrusor activity during filling and voiding.

Although early irritative bladder symptoms have been described in patients with bladder dysfunction due to prolapsed lumbar discs, presentation with an uninhibited type of neuropathic bladder dysfunction (demonstrated by cystometry), and without loss of bladder sensation, has not previously been reported. We feel that this represents the first stage in a progressive disorder of bladder function due to increasing involvement of the cauda equina, which contains the nerve fibres connecting the bladder to the spinal centre in the medullary cone. Irritation of the cauda equina may initially or, with less severe degrees of compression, produce hyperexcitability of the sensory and motor fibres resulting in irritative symptoms and an uninhibited bladder. More severe or progressive compression leads to loss of bladder sensation, atonicity and difficulty in voiding, culminating ultimately in chronic painless retention.

Sudden massive prolapse may lead to acute urinary retention with classical disc symptoms.

It is possible that as the cauda equina also contains the fibres controlling the external sphincter mechanism, disc lesions may produce disturbances of micturition due to sphincteric dysfunction. We believe that the condition is quite common. In addition to the 5 cases reported, several others have been encountered in this hospital during the past few months.

We wish to acknowledge with grateful thanks for their assistance: Mr Richard Johnson, Director, Department of Neurosurgery, and Dr Robert Ollerenshaw, Director, Department of Medical Illustration at Manchester Royal Infirmary.

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A Urodynamic View of the Clinical Problems associated with Bladder Neck Dysfunction and its Treatment by Endoscopic Incision and Trans-trigonal Posterior Prostatectomy¹

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The evaluation of urodynamic function by symptomatology, clinical examination, static radiography and endoscopy is considerably less reliable than is sometimes appreciated.

Since the establishment of our Urodynamic Clinic we have reviewed more than 6,000 patients with dysfunctional voiding (Turner-Warwick and Whiteside, 1969); synchronous cine/pressure/flow cystography has been used in the last 3,000 of these (Bates, Whiteside and Turner-Warwick, 1970). This communication is an attempt to summarise some aspects of our present thinking related to problems of bladder neck dysfunction and outflow impairment.

In considering bladder outflow obstruction we must seriously question some commonly held precepts relating to the significance of various facets: symptomatology; the absence of post-voiding residual urine; the endoscopic evaluation of the bladder neck; trabeculation of the bladder; the actual size of the prostate; etc.

Terminology

Many of the terms commonly used to describe bladder neck obstruction seem to place inappropriate emphasis on static rather than dynamic considerations; the hypertrophied state suggested by "bladder neck hypertrophy" and "median bar" is as irrelevant to the underlying nature of the problem as the fibrosis suggested by the terms "bladder neck contracture" and *sclérose du col*". Dysfunctional inefficiency of the bladder neck opening is perhaps better described by the term "dyssynergic bladder neck occlusion".

The "internal sphincter" can be accurately referred to as the bladder neck; the so-called "external sphincter" tends to focus attention on the extrinsic striated muscle component while the term "distal sphincter mechanism" clearly includes the important intrinsic urethral complex (Fig. 1).

Bladder Neck Function and Dysfunction

The normal bladder neck is an important sphincter: it lies closed at rest, it is cough-competent and it is not normally opened by straining. It is not a separate concentric muscle but an arrangement of the lower fibres of the detrusor and trigonal musculature. Isolated sphincter studies in

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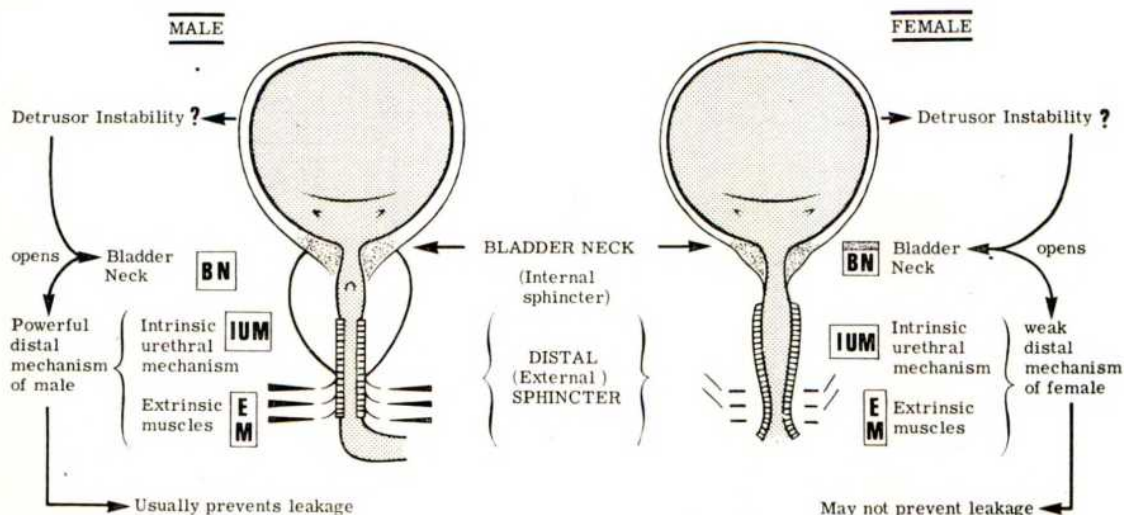


Fig. 1. Comparison of the bladder and sphincter mechanisms in the male and female.

both male and female show that alone it can maintain continence and the patient may even interrupt a voiding stream, albeit somewhat slowly, by inhibiting the detrusor mechanism and thus allowing the bladder neck to close (Turner-Warwick, 1971).

The normal opening mechanism of the bladder neck is related to detrusor and trigonal function and it seems probable that dyssynergic failure of bladder neck opening is commonly the result of a dysfunctional arrangement of the bladder neck musculature inherent in its development; this conception is supported by the lifelong nature of the condition. The actual mechanism is a separate consideration.

Life History

The state of sacculated decompensation of the bladder, sometimes referred to as "Marion's Disease", seems to be the end-result of a mild but critical degree of lifelong bladder neck obstruction rather than a "small fibrous prostate".

The life progress of the bladder state of a patient with such a mild but significant dyssynergic bladder neck occlusion is illustrated in Figure 2. At the age of 50 the history would have indicated that the patient had had a "non-competitive stream" with a tendency towards a "hesitant start" throughout his life—he just did not go in for that sort of game at school! This degree of obstruction would have been difficult to diagnose on the basis of routine urological investigation at the age of 10, 20 or 30; it would have been possible to identify it urodynamically but this would probably have been academic since, in the absence of recurrent infection or troublesome symptoms, it would not have required treatment. The fact that the patient has never experienced a powerful voiding stream often tends to mask the history, sometimes to a point at which he may strenuously deny there could be anything wrong with it.

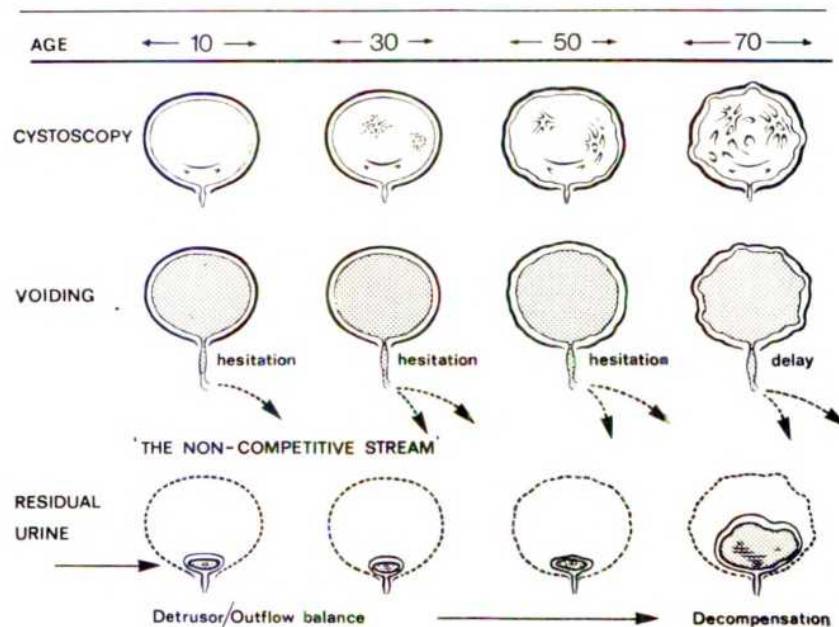


Fig. 2. The life progress of dyssynergic bladder neck occlusion.

Age Incidence

The age incidence of patients attending with bladder neck obstruction necessarily depends upon the diagnostic criteria; the incidence of a small consecutive group in our series who have required treatment and who have been investigated both pre- and post-operatively is illustrated in Figure 3. These clearly represent patients in whom the voiding imbalance is mild compared with those who must have presented as a result of gross imbalance during childhood and the apparent diminution in the elderly may have resulted from masking of the diagnosis by gross prostatic enlargement.

Symptomatology

The majority of patients presenting as a result of bladder neck imbalance complain of symptoms suggesting a urodynamic problem; urgency, frequency, nocturia, dysuria, delay, poor stream, dribbling, etc.; in others the nature of the problem is less obvious. Recurrent urinary infection in the male or difficulty with voiding after operation or medication suggest the need for urodynamic assessment, as also does a history of difficulty with voiding in the company of others at a public urinal (many such patients have previously been referred for psychiatric advice but in reality have an easily treatable condition). Overlapping symptomatology may result in a diagnosis of "prostatitis".

A significant number of patients may be virtually asymptomatic; some even strenuously deny abnormality in spite of a degree of bladder outflow obstruction requiring urgent treatment. Even with considerable experience of the cross-correlation of symptoms and urodynamic findings it is often difficult to make or to exclude a diagnosis on the basis of a history, and a high degree of suspicion is required in order to avoid missing a significant outflow obstruction.

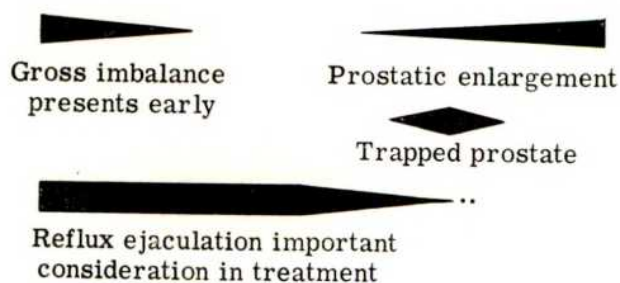
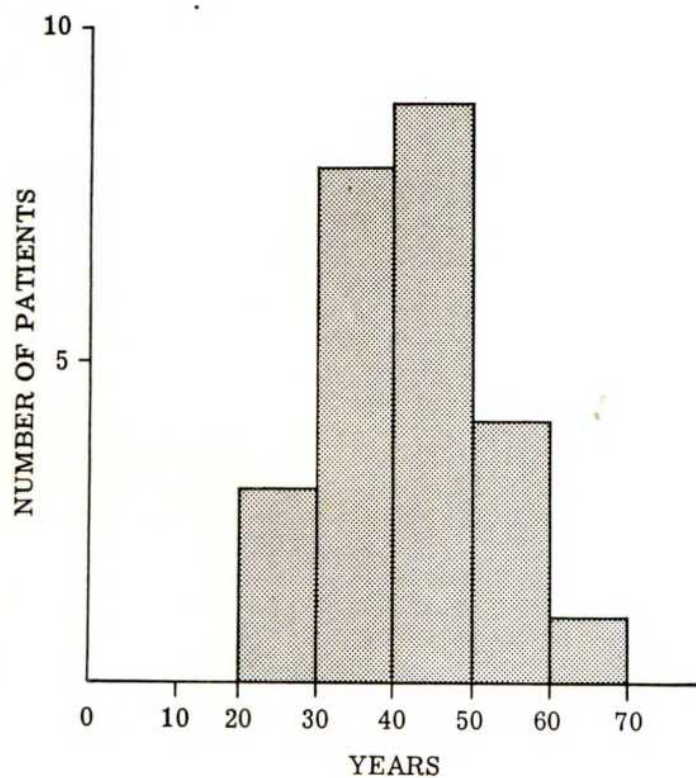


Fig. 3. Age distribution of adult patients with dyssynergic bladder neck occlusion requiring treatment in an adult clinic. The diagnosis in the elderly is likely to be obscured by gross prostatic enlargement.

Clinical Examination

The actual size of a prostate, whether or not it is enlarged, is basically unrelated to the diagnosis or degree of outflow obstruction.

Endoscopic Evaluation

It is particularly important to question the interpretation of the endoscopic appearances of trabeculation. In the male, extensive trabeculation usually indicates a degree of detrusor hypertrophy, increased bladder wall thickness and a raised detrusor pressure; it is commonly caused by obstruction due to a dyssynergic bladder neck, prostatic enlargement or urethral stricture, but it may equally result from an unstable bladder of either a primary or a neuropathic type.

In the female, trabeculation does not necessarily indicate hypertrophy; it is often associated with a thin-walled bladder and a normal or even low detrusor pressure. True bladder wall hypertrophy in the female is not easy to distinguish endoscopically and it is more commonly the result of an unstable systolic bladder of a primary or a neuropathic type than of outflow obstruction (Turner-Warwick, 1971). The bladder neck is a remarkably rare cause of outflow obstruction in the female.

Dyssynergic bladder neck occlusion is not an uncommon condition in the male and the *advanced* state can usually be identified with a fair degree of accuracy provided the limitations of the individual parameters of assessment are recognised. It is, however, of fundamental importance to appreciate that the combination of the cysto-urethrosopic appearance of trabeculation and bladder neck hypertrophy does not necessarily constitute bladder neck obstruction either in the male or the female. Global hypertrophy of a normally synergic detrusor/bladder neck opening mechanism, resulting from a distal stricture, does not result in a dyssynergic bladder neck occlusion and erroneous treatment as such may compromise a subsequent urethroplasty.

The behaviour of a bladder neck opening mechanism cannot be evaluated accurately by endoscopic observation, for no amount of urethrosopic observation or manipulation of the bladder neck, whether hypertrophied or not, will enable the observer, however experienced, to guess or deduce accurately whether it will open satisfactorily or remain closed when the detrusor contracts.

Intravenous Urography

The intravenous urogram may provide evidence of bladder outflow obstruction, but normal appearances cannot exclude it. A significant bladder outflow obstruction requiring treatment is frequently found in patients with no post-voiding residual urine; the presence of such a residual is better regarded as evidence of decompensated bladder failure and it seems advisable, on urodynamic grounds, that this state of affairs should be anticipated and avoided.

In point of fact, a residual urine does not develop until a relatively late stage in adults with dysynergic bladder neck occlusion; presumably this is the result of the fine degree of the imbalance between the bladder wall and the bladder neck and, since this is created by a single muscle mechanism, hypertrophy can progress to an advanced stage, without disturbing the balance, before decompensation finally occurs.

The Voiding Flow Pattern

Not only is a patient's evaluation of his own stream often misleading as a result of becoming accustomed to a lifelong state, but also the observation of the stream, whether directly or radio-graphically, may be misleading unless it is obviously excellent.

The recording flow-rate meter is clearly the most important clinical screening test for the detection of outflow obstruction and the record of this can be preserved in the patient's notes (Fig. 4). It is important to appreciate, however, that the flow rate is only one of the parameters necessary for evaluating voiding efficiency; it provides essential data, but the pattern must not be over-interpreted.

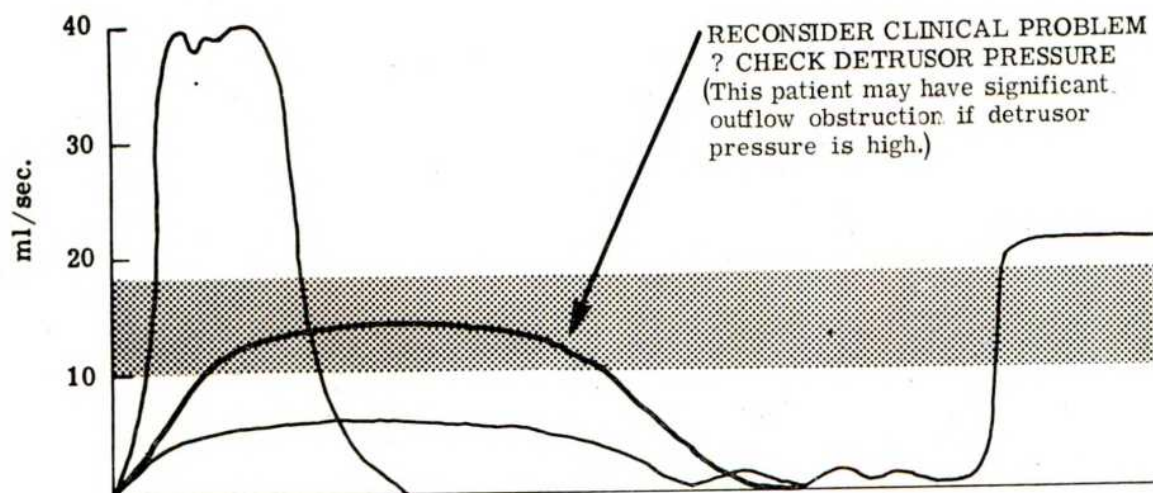
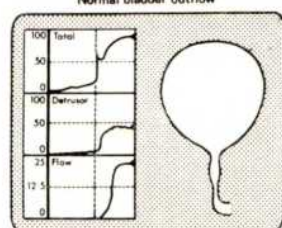


Fig. 4. Voiding flow-rate patterns. The top curve shows efficient voiding (some patients with high curves have hypersystolic detrusor states). The middle curve lies within the range of suspicion, the patient may have significant outflow obstruction if the detrusor pressure is high. The bottom curve is abnormally low; clearly indicating voiding inefficiency.

NORMAL BLADDER NECK — DETRUSOR OPENING MECHANISM

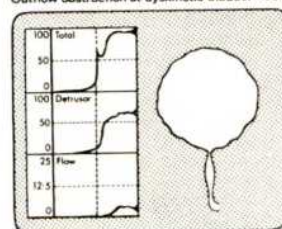
Normal bladder outflow



(A)

LIFE-LONG DYSKINETIC IMPAIRMENT OF BLADDER NECK OPENING MECHANISM

Outflow obstruction at dyskinetic bladder neck



(B)

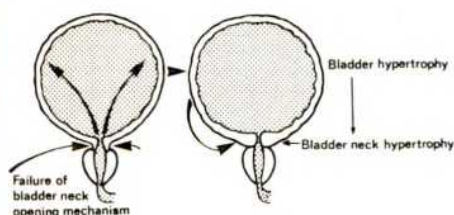


Fig. 5. (A) Pressure flow cysto-urethrogram illustrating a normal detrusor bladder neck opening mechanism with efficient voiding. (B) Outflow obstruction resulting from failure of bladder neck opening due to dyssynergic detrusor mechanism. Diagram illustrates the consequent global hypertrophy.

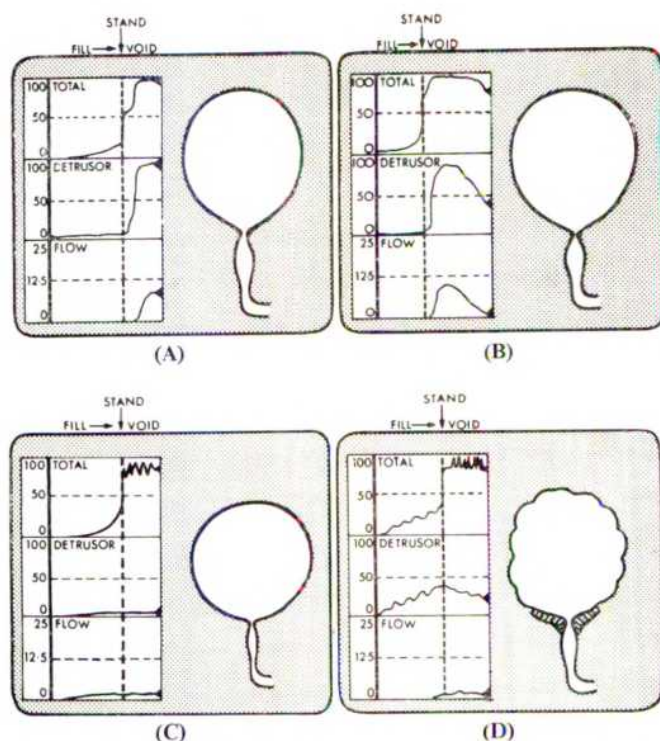


Fig. 6. Abnormalities of detrusor/bladder neck opening mechanisms. (A) Dyssynergic bladder neck occlusion probably resulting from morphological arrangement of detrusor/trigonal musculature. (B) Decompensated detrusor failure resulting in detrusor fading and premature bladder neck closure. (C) Low activity ("atonic") detrusor states resulting in failure of bladder neck opening. (D) Iatrogenic dyssynergia resulting from replacement of normal detrusor by bowel cystoplasty.

Urodynamic Evaluation

In a urodynamic clinic we are often concerned with the accurate identification of the less obvious but nevertheless clinically important abnormalities of bladder neck function.

Resting urethral pressure-profile measurements have been disappointing in the identification of some of these and this is perhaps hardly surprising since one is seeking to determine the behaviour of a bladder neck resulting from a detrusor contraction, not its static closing pressure when the detrusor is relaxed.

This emphasises the importance of synchronous estimation of the state of the detrusor in relation to the flow rate and/or cysto-urethrography for the interpretation of the bladder neck behaviour whenever it fails to open, or remains open (Fig. 5); one which appears to lie open on simple cystography is not by any means necessarily abnormal, it may be wide because the normal detrusor opening mechanism is momentarily contracting.

A general urodynamic view of normal and dyssynergic bladder neck occlusion is illustrated in Figure 5; it seems likely that the inefficient bladder neck opening mechanism creates the relative outflow obstruction to which the bladder responds by global hypertrophy and, since the bladder neck is morphologically identical, it naturally hypertrophies, *pari passu*.

While it seems probable that the common type of lifelong dyssynergic failure of bladder neck opening is the result of the morphological arrangements of the detrusor/trigonal musculature in

that individual, obstructive failure of bladder neck opening may be seen in various other conditions (Fig. 6). Progressive "fall-off" of detrusor contraction during voiding is characteristic of obstructive detrusor decompensation and certain types of neuropathy; not infrequently this results in premature bladder neck closure and contributes to a residual urine. Iatrogenic failure of bladder neck opening may occur as a result of replacement of a previously normal detrusor/bladder neck opening mechanism by a bowel cystoplasty (Turner-Warwick, 1970, 1971). Among patients considered clinically to have an "atonic bladder" are many with normal or even high activity detrusor states; some, however, prove to have low activity detrusor states, and while many of these have a patulous bladder neck a few seem to develop relative obstruction at the bladder neck as a result of failure of the opening mechanism.

Endoscopic Diathermy Incision of the Bladder Neck

Bladder neck obstruction is commonly treated by endoscopic loop resection or VY-plasty; both quite often result in reflux ejaculation, and loop resection carries an additional risk of secondary bladder neck contracture.

We now routinely treat this condition by endoscopic diathermy incision, cutting through the bladder neck with a flat-sided resectoscope knife electrode in the 4 o'clock and 8 o'clock position from the bladder base to the verumontanum (Fig. 7). The incision tends to spring apart as the extravesical plane is approached, and at the end of the procedure, review from the level of the verumontanum shows that the bladder neck lies wide open as if several loopfuls of tissue had been resected from either side. The posterior margin of the bladder neck appears prominent, somewhat resembling a middle lobe, but the instinctive urge to resect this is better resisted because it does not cause a urodynamic obstruction and may account for the relatively low incidence of subsequent reflux ejaculation.

We have been impressed by the clinical results of this procedure in a series of more than 70 patients over the past 5 years and a detailed urodynamic analysis of a consecutive group of these will be published separately (Milroy, Cairns, *et al.*); a typical urodynamic assessment is shown in Figure 7. The relief of bladder neck occlusion on voiding has been reliably effective and apparently lasting; it is of interest that although the bladder neck opens widely on voiding it is usually occlusive at rest.

Complications have been few; we maintain catheter drainage for a few days since the bladder neck is frequently transected to expose perivesical fat, but we have not yet been troubled by extravasation. Subsequent re-insertion of the catheter for evacuation of retained clot has occasionally been necessary. Reflux ejaculation may undoubtedly occur and must always be discussed with the patient pre-operatively, but the incidence of this appears relatively low and this is an important consideration in view of the age-group in which an occlusive bladder neck may require treatment.

It is remarkably difficult to obtain a partial relaxation of a dyssynergic occlusion of the bladder neck mechanism to a point at which it becomes nonobstructive and yet competent; fortunately prevention of reflux ejaculation is a less critical measure of proximal posterior urethral closing. When, however, the avoidance of reflux ejaculation is of particular importance to a young patient requiring bladder neck relaxation we are inclined to try a partial bladder neck incision, stopping short of complete transection and evaluating the results of this urodynamically before proceeding further if necessary; among these are the only patients in our series who have so far required re-incision and we have not yet seen secondary bladder neck contracture.

The inherent problem of partial-thickness incision is not only the difficulty of estimating the thickness of the bladder neck that remains uncut (until the extravesical plane is reached!) but also its potential efficiency.

In view of our encouraging experience with the incisional procedure we find it difficult to understand why Collins' panendoscope knife is not more widely used for bladder neck incision in place

of the potentially more complicated loop resection (though we in fact prefer to use a knife electrode adapted for a resectoscope).

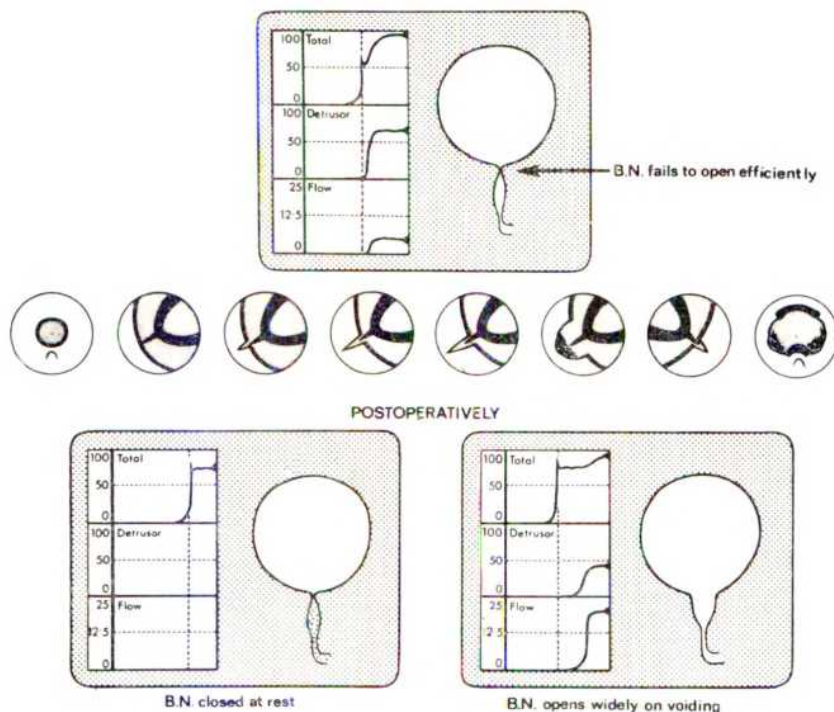


Fig. 7. Selective bladder neck relaxation by endoscopic diathermy incision. The bladder neck is progressively incised in the 4 o'clock and the 8 o'clock positions from the bladder base to the verumontanum using a flat-sided knife electrode. As the incision approaches complete transection the incision tends to open. At the completion, review from the verumontanum shows a wide open bladder neck with anterior and posterior urothelial bridges. Postoperative pressure flow cystourethrography commonly shows that the bladder neck lies closed at rest and opens wide on voiding, which is achieved at a normal flow rate.

Indications and Contra-indications

The indication for bladder neck incision is the need to relieve a urodynamically proven bladder neck occlusion; in spite of the fact that the incidence of reflux ejaculation appears to be relatively low, the possibility should always be taken into account.

The normal distal urethral mechanism in the male is reliably competent and continence is not normally compromised by bladder neck relaxation; if, however, the distal mechanism is not normal, bladder neck ablation may result in urinary incontinence.

The surgical management of a urethral stricture, for instance, may be seriously compromised if the secondary hypertrophy of the bladder neck, resulting from the global hypertrophic response to the outflow obstruction due to the stricture, is mistakenly diagnosed endoscopically as a dyssynergic bladder neck occlusion and consequently ablated. This is particularly important if the stricture extends into the distal urethral mechanism, for a surgical repair will then risk subsequent incontinence since many patients depend upon their bladder neck function for their continence after a trans-sphincter urethroplasty (Turner-Warwick, 1969). Hypertrophy of a normally functioning bladder neck mechanism due to a distal obstruction does not create a dyssynergic bladder neck function.

Early Prostatic Enlargement and Bladder Neck Obstruction: the "Trapped Prostate"

If a patient with a bladder neck occlusion develops early prostatic enlargement (Fig. 8), it commonly creates an exacerbation of symptoms.

The bladder neck abnormality and early prostatic enlargement appears to summate to create a significant obstruction when, but for pre-existing bladder neck abnormality, the relatively unimpressive degree of prostatic enlargement would be unlikely to cause trouble.

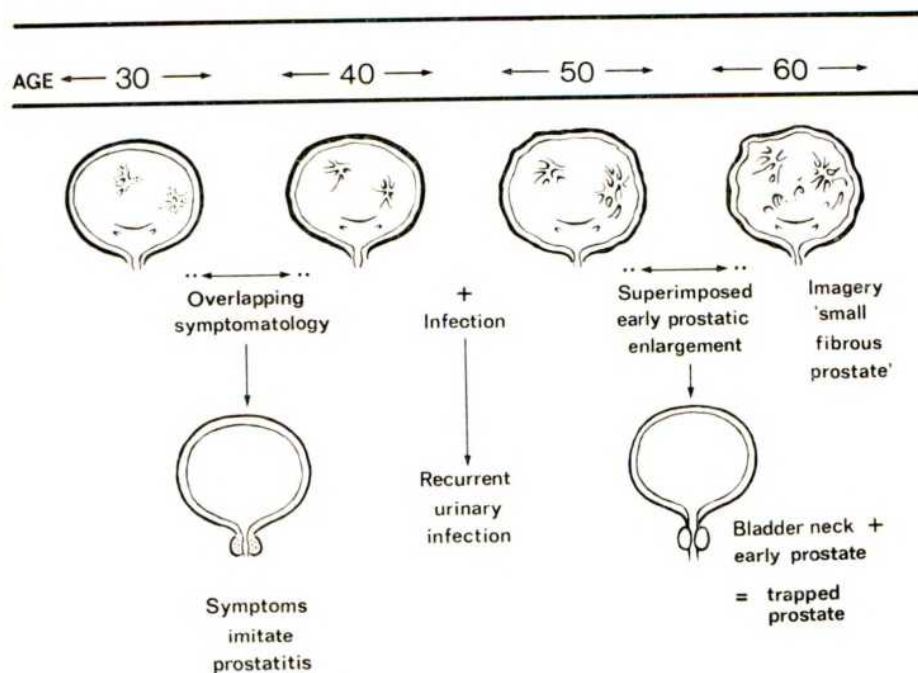


Fig. 8. Clinical manifestations associated with dyssynergic bladder neck occlusion.

If such a patient seeks advice he is often reassured on the basis that his prostatic enlargement is minimal and that he has no residual urine. Careful enquiry may, however, reveal a pre-existing history suggesting a long-standing outflow impairment, and endoscopy is likely to show early enlargement of the lateral lobes of the prostate encroaching upon the prostatic urethra beneath an occlusive bladder neck; in many cases the diagnosis requires a confirmatory urodynamic flow-pattern study, and ideally this should be a clinic routine.

It is frequently difficult to distinguish between obstruction due to prostatic enlargement and the "trapped prostate" on the basis of voiding cysto-urethrography and indeed it is sometimes difficult to distinguish either of these from pure bladder neck obstruction unless a reasonably capacious prostatic urethra is seen or Whiteside's sign is present (failure of retrograde prostatic urethral emptying resulting from premature bladder neck closures common in dyssynergic bladder states: this test also shows the distensibility of the prostatic urethra).

The trapped prostate can be effectively treated by endoscopic loop resection or by any open surgical procedure suited to the smaller prostate.

In selected cases we have elected to treat the bladder neck element by deep endoscopic incision endeavouring to "release" the otherwise unimpressive prostatic enlargement. Apart from its

simplicity this treatment has particular advantage for the patient who wishes to postpone prostatectomy in order to procreate; the results are probably greatly dependent on the assessment of the individual case, it has sometimes been necessary to proceed with prostatectomy at an early date, but the immediate urodynamic result and short-term follow-up of the cases in our small series has been satisfactory.

“Prostatitis” and Bladder Neck Obstruction

“Prostatitis” is a difficult disease to specify; many patients so diagnosed suffer from an infected prostate, others complain of dysuria, frequency, urgency, “bladder awareness”, radiating pains and discomfort, and prove to have no definable abnormality apart from a prostate which may be considered to be “boggy”.

Diagnostic confusion sometimes arises as a result of symptomatic overlap with bladder neck dysfunction, and it is well worth while screening this group of patients for outflow obstruction, at least by a voiding flow record: bladder neck obstruction is much easier to relieve than prostatitis.

The “Small Fibrous Prostate”

The “small fibrous prostate” appears to some extent an imagery and even a phantasmagoric diagnosis. The prostate so diagnosed may not itself be abnormal although not uncommonly evidence of non-specific inflammatory change may be found: it rarely seems to cause a urodynamic obstruction and if obstruction is present this is likely to be due to dysfunction of the bladder neck above it or of the distal urethral mechanism.

The image it conjures for the resectionist is, of course, the risk of secondary obstructive sclerosis, while that for the would-be enucleationist is the additional impossibility of achievement and the difficulty of excision.

Trans-Trigonal Posterior Prostatectomy

Removal of a relatively small prostate is not infrequently required for prostatitis or extensive calculi. This can be achieved relatively simply by trans-trigonal posterior prostatectomy with reconstruction, utilising the pre-vesicle plane (Turner-Warwick, 1968) (Fig. 9).

The inter-ureteric bar is divided in the midline to expose the vesicles and the posterior lobe of the prostate is dissected forwards in the pre-vesicle plane until the prostatic urethra is entered just above the verumontanum, with an appropriate sharp resection of the lateral prostatic tissue. The removal of the posterior lobe facilitates occlusion of the bare area.

Dyssynergic Distal Urethral Obstruction

Urodynamic evaluation indicates that a dyssynergic or hypertonic type of outflow obstruction may occur in relation to the intrinsic distal urethral mechanism; this is an occasional cause of residual outflow obstruction after bladder neck incision/resection and prostatectomy (assuming that stricture and residual prostatic tissue, the commoner causes of residual distal urethral obstruction, have been definitively excluded). This functional obstruction can be relieved by selective Otis sphincterotomy (Fig. 10). We recalibrate the distal urethra cautiously in 10F steps, with careful urodynamic evaluation after an interval of several weeks between each 10F step until such time as efficient voiding is re-established, in order to avoid impaired control.

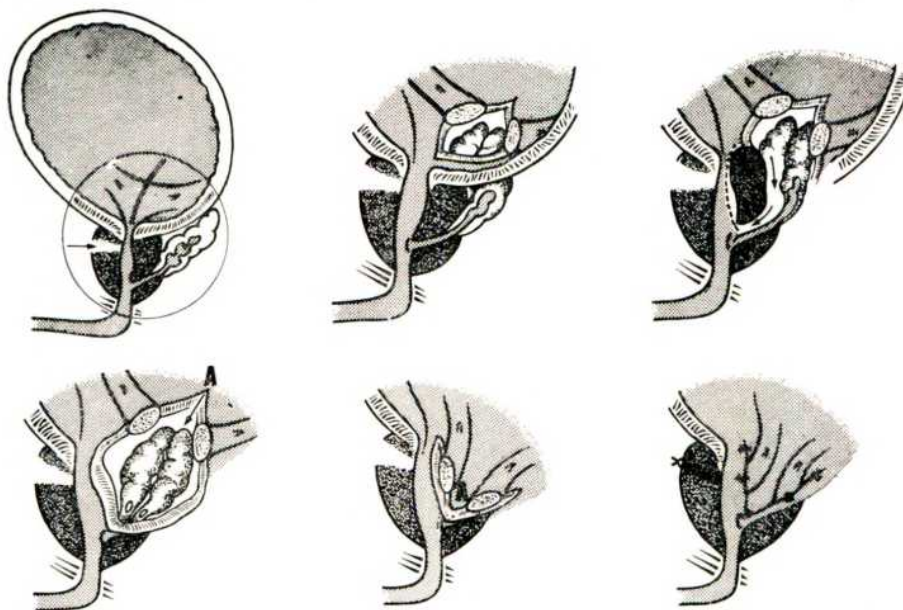


Fig. 9. Trans-trigonal posterior prostatectomy with reconstruction. The upper prostatic urethra is opened anteriorly just below the bladder neck. The interureteric bar is divided in the midline to expose the vesicles, the bladder neck and posterior lobe of the prostate are dissected forward in front of the pre-vesicle tissue plane until the urethra is entered just above the verumontanum; synchronous sharp resection removes the inner part of the lateral prostate. The upper end of the interureteric incision is approximated to the verumontanum and the divided ends of the prostatic capsule is sutured on either side to occlude the prostatic urethral defect. The anterior prostatic capsule is closed.

Obstructive Detrusor Instability

The detrusor muscle may respond to obstruction by the development of unstable (uninhibited) systolic contractions; the filling cystometrogram may be virtually indistinguishable from a neuropathic pattern and this unfortunately prevents forewarning of a coincident neuropathy by urodynamic evaluation (Fig. 11).

Obstructive detrusor instability usually resolves after relief of the obstruction irrespective of whether this was due to the bladder neck, the prostate, the distal sphincter mechanism or a stricture (Fig. 11b); obstructive detrusor instability may persist in spite of uroynamically proven relief of obstruction and it represents an important cause of persistence of symptoms; frequency and urgency are commoner than leakage owing to the relative efficiency of the normal distal urethral mechanism in the male.

The possibility of persistent instability may represent a cogent reason for advising early treatment of an established outflow obstruction associated with an unstable bladder in order to prevent the progressive hypertrophy, and consequent high detrusor pressures, which might further compromise the result in the event of a persistent detrusor instability following the relief of obstruction.

Bladder Neck Occlusion in the Female

Obstruction at the level of the bladder neck has proved to be a remarkably rare cause of female bladder outflow obstruction in our series, probably in the region of 1 per cent (Fig. 12). The incidence seems to be higher among diabetics, and patients with a very low detrusor activity may develop relative outflow obstruction at this level owing to failure of the bladder neck opening mechanism (Fig. 6c). The absence of an effectively competent bladder neck mechanism in the

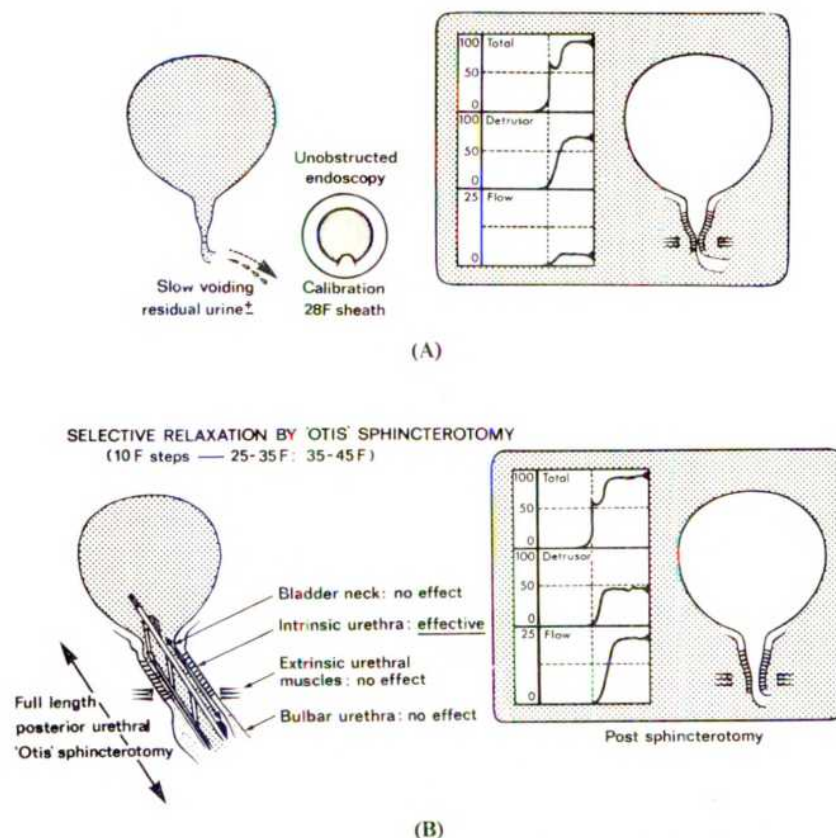


Fig. 10. Post-prostatectomy outflow obstruction due to hypertonic distal sphincter. (A) Poor stream and residual urine persistent after relief of bladder neck and/or prostatic obstruction, stricture and residual prostatic tissue excluded by endoscopy, pressure/flow cystogram shows obstruction associated with distal mechanism. (B) Selective relaxation by Otis sphincterotomy, recalibration in 10F steps with urodynamic re-evaluation between each. Full-length posterior urethral Otis sphincterotomy has negligible effect on bladder neck and extrinsic urethral muscles thus achieving selective intrinsic urethral relaxation; post-sphincterotomy pressure/flow cysto-urethrogram shows restoration of voiding.

female, whether due to natural incompetence, ablation or detrusor instability (Bates *et al.*, 1971), predisposes to stress incontinence since the distal urethral mechanism is very much less reliably efficient than it is in the male (Fig. 1).

Anterior Relaxation of the Bladder Neck in the Female

The female bladder neck is often relatively thin compared with that of the male. Anterior incision not only avoids the risk of subsequent fistulation into the vaginal vault which may follow posterior or postero-lateral incision, but it also offers the possibility of retropubic re-closure in the event of troublesome incontinence after bladder neck relaxation. We use a single midline incision anteriorly, into the bladder neck and the upper third of the urethra, performed under direct vision through a long bladed, self-retaining nasal speculum, or, preferably, a fibre-lit posterior urethral retractor. Anterior incision can of course be achieved endoscopically with a knife electrode, but a loop resection is likely to compromise the chance of anterior reconstruction.

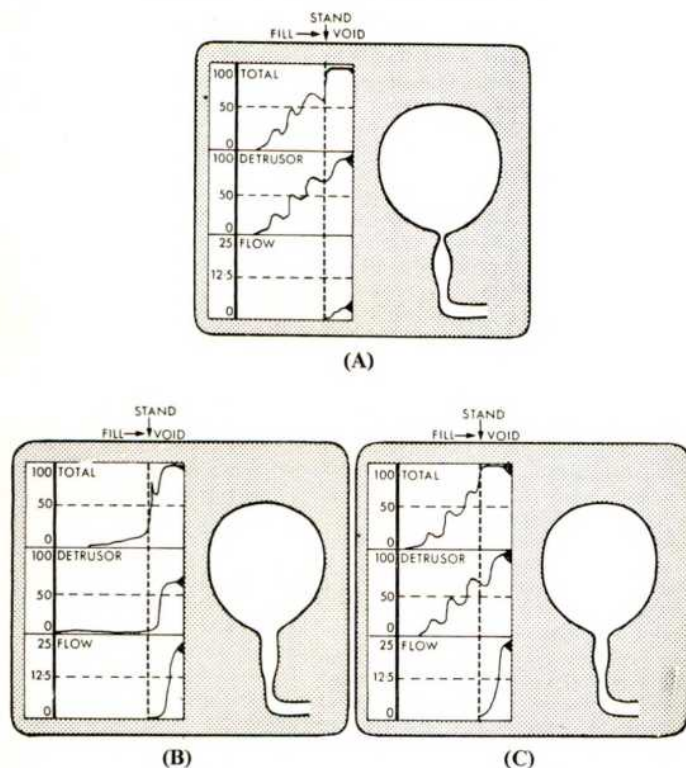


Fig. 11. Obstructive detrusor instability. (A) Pressure flow cystourethrogram showing uninhibited detrusor contractions during the filling phase in a patient with outflow obstruction due to dyssynergic bladder neck occlusion. (B) After relief of obstruction the detrusor instability usually resolves. (C) If detrusor instability does not resolve urgency and frequency persist and leakage may occur if the distal sphincter mechanism is unable to contain the elevated detrusor pressures. Residual outflow obstruction and neuropathy must be excluded if instability persists.

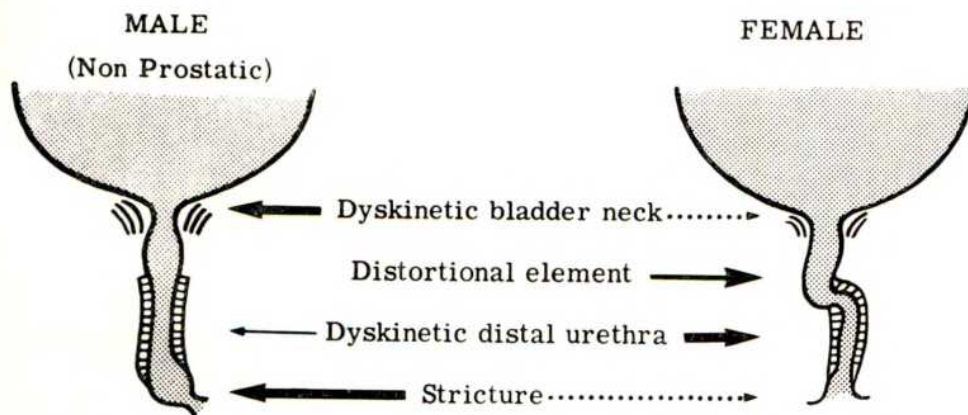


Fig. 12. Diagrams compare the relative incidence of elements of outflow obstruction in male and female (excluding neuropathy and prostatic obstruction).

VY-plasty is useful for the treatment of secondary bladder neck sclerosis, but seems an unnecessarily extensive procedure to relax a simple dyssynergic bladder neck occlusion; the comparative rarity of this condition in the female suggests that the beneficial results of VY-plasty quite often are due to its additional effect upon the distal urethral mechanism of the female.

Conclusion

Objective urodynamic proof beyond endoscopic evaluation is often required, both to make and to exclude a diagnosis of bladder neck obstruction. Once an impaired outflow is proven, a voiding cysto-urethrogram provides reliable information as to its level.

Bladder neck obstruction is in fact a relatively rare cause of outflow obstruction in the female; the bladder neck mechanism represents the primary defence against stress incontinence and, since the distal mechanism is unreliable, it should not be ablated without objective evidence that it is obstructive.

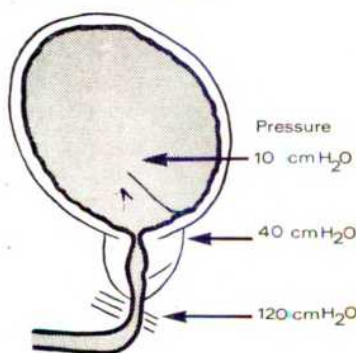
Apart from considerations of reflux ejaculation, bladder neck ablation in the male is less critical to effective urinary control because the distal mechanism is reliably competent provided it is normal. If, however, the "diagnostic" appearance of bladder neck obstruction was in reality the result of distal obstruction due to a stricture rather than a dyssynergic bladder neck occlusion, its erroneous ablation may compromise the definitive surgical treatment of the stricture owing to the risk of incontinence after a urethroplasty involving the distal mechanism.

Discussion

C. P. Bates, (on behalf of E. P. Arnold, D. E. Griffiths and himself). I wish to present some evidence in support of the contention that the underlying abnormality in bladder neck obstruction

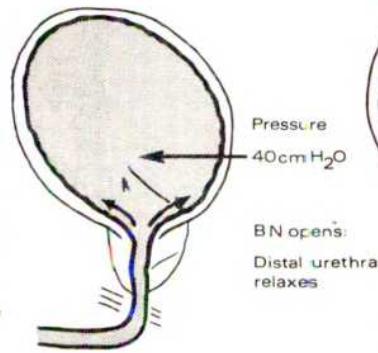
AT REST:-

Normal and obstructed patients.



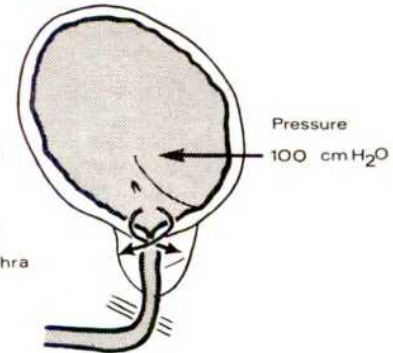
VOIDING:-

Normal patients.



VOIDING:-

Bladder neck obstruction.



without prostatic enlargement is one of disordered function, rather than a simple mechanical obstruction.

We have measured the closing pressure of the urethra by the method of Brown and Wickham, using a 12 or 14F catheter. In this way we have measured the passive squeeze of the bladder neck at rest in both normal and obstructed patients, and compared this with the peak detrusor pressure during micturition (see figure).

Somewhat to our surprise we found little difference between the resting pressure at the bladder

neck in normal patients and those shown to have obstruction by subsequent cine pressure studies. However, the important feature was that in obstructed patients the pressure in the bladder during micturition was always substantially higher than the pressure at the outlet at rest. The implication of this finding is that instead of the bladder neck being actively opened as is said to occur normally, in the early cases of obstruction studied here, it not only fails to open but appears to be actively tightened.

The accompanying diagram illustrates this and gives approximate mean levels of detrusor pressure (with abdominal pressure subtracted).

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The Wide Bladder Neck in Children¹

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During the last 3 years, the Incontinence Unit at the Institute of Urology has investigated over 100 selected children with persistent diurnal urinary incontinence in whom simple remedies had failed. The sole physical finding in 21 of those children was a wide bladder neck and the object of this investigation was to determine whether a wide bladder neck was a specific disorder. The condition may be recognised by one or more of the following signs:

1. Widening of the bladder neck on a micturating cystogram.
2. Incomplete milk-back on a micturating cystogram.
3. An open bladder neck on cystoscopy.
4. A low urethral pressure profile.
5. A normal cystometrogram, and absence of neurological signs.
6. Absence of distal urethral stenosis.

Material. Over 100 cases of diurnal and nocturnal incontinent children were investigated. A history was taken and a general and neurological examination performed. Investigations included an MSU, IVP, micturating cystogram (MCG), cystoscopy under general anaesthetic, urethral pressure profile and a cystometrogram. All enuretics were excluded.

The micturating cystogram was carried out by intermittent screening, and exposures were made on a 70-mm film with a total gonadal radiation dose below 200 mr. The urethral pressure profile was performed as described by Harrison and Constable (1970). The filling cystometrogram was carried out in the standard way. The bladder was filled with normal saline at a rate of 50 ml per minute via a No. 8 Porges urethral catheter. A fine epidural catheter was placed alongside this and connected to a transducer, and the rise of bladder pressure was recorded on a single channel XY Recorder. A separate rectal pressure line was not used as it was felt this would not be acceptable to the child.

Findings

21 children were found to have a wide bladder neck on one or other of the criteria already mentioned. Four of the children were male. Their average age was 9 years and 9 months. One interesting fact emerged from the history, namely that 9 children had symptoms of onset following a period of urinary continence. They all had diurnal incontinence and in addition 10 of the children had nocturnal incontinence. No gross anomalies of the urinary tract were found and the external meatus and urethral lengths were all normal.

The micturating cystogram was found to be the most useful investigation and, as the results show, the most accurate. A wide bladder neck can be objectively demonstrated, as can incomplete milk-back. Both are believed to be evidence of failure of the intrinsic urethral mechanism. Conversely, in a series of micturating cystograms performed on children with conditions other than

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

incontinence, the presence of a wide bladder neck was not noted. The micturating cystogram (Table I) demonstrated a wide bladder neck at rest in 16 children, of whom 5 also had incomplete milk-back and 10 had cystoscopic confirmation of a wide bladder neck. Of the remaining 5 cases, 3 had a closed bladder neck and demonstrated incomplete milk-back or stress incontinence, 1 was normal and 1 was unable to void.

Cystoscopic confirmation of a wide bladder neck is subjective and depends on several factors, including the depth of anaesthesia, the amount of fluid in the bladder and the rate of flow from the urethroscope. The presence of longitudinal folds when the bladder is empty, which disappear on filling, is suspicious. Closure of the bladder neck may be obtained with simple perineal electrical stimulation.

A wide bladder neck was found during 14 cystoscopic examinations (Table II). There were 5 patients in whom a wide bladder neck was shown on micturating cystogram and not confirmed by cystoscopy. The remaining 2 cases demonstrated incomplete milk-back.

The urethral pressure profile provides a new objective assessment of urethral resistance and therefore of urethral bore (La Place's Law); however, this is not easy to perform with consistent accuracy in a conscious child and in 10 out of the 19 cases it was performed under a general anaesthetic (Table III). Because of this, the result bears less relationship to the normal physiological state and its interpretation is more difficult. A normal urethral pressure profile in this age-group has been taken to be above 80 cm of water. 11 out of 19 children had a urethral pressure profile below this figure, either whilst conscious or under a general anaesthetic. The average conscious profile pressure was 57 cm and unconscious it was 42.5 cm.

A conscious filling cystometrogram was performed in 13 cases and was normal in all. It was carried out under a general anaesthetic in all but one of the remainder.

Two intravenous pyelograms were abnormal: one showed a minor congenital abnormality of the renal pelvis and the other demonstrated chronic pyelonephritis.

Four children had an infected urine at one stage or other of their investigations. In 2 there was no associated pathology, one had chronic pyelonephritis and the other had reflux.

Results of Treatment. Because there was no obvious indication for surgery and the natural history of the disorder was unknown, conservative treatment was followed in all cases (Table IV). Cetiprin (emeprium bromide) and Tofranil (imipramine) were the most commonly used drugs. The former blocks peripheral cholinergic and ganglionic transmission and increases bladder capacity and delays the first desire to void. It produced improvement in 4 out of 5 children in an average time of 10 weeks. Tofranil, which is believed to act centrally, produced an improvement in 6 cases over an average time of 9½ weeks. There were no failures. Neither drug was continued for longer than 6 months.

The anal plug was used in 6 patients, 3 improved in 10 weeks and 3 were unchanged. The 3 who were improved by the plug are no longer using it.

The 2 cases that came to surgery had both been treated conservatively. One patient had bilateral reflux and an infected urine, and a bilateral re-implantation and tightening of the bladder neck was performed. When reviewed 4 months after the operation, she was both continent and free from urinary tract infections. The other child had been treated unsuccessfully with Tofranil, an anal plug, a sling and finally a stimulator. She was still incontinent. One case, a girl of 15, was treated successfully with a pubi-vaginal spring, the remaining case was having no treatment and was still under review.

These cases have been followed for varying periods. 15 have improved and 5 have shown no benefit and 1 is still awaiting follow-up.

Discussion

Persistent day-time incontinence in older children is a relatively uncommon symptom and it has long been recognised (De Backer and Williams, 1962) that some of these children have a wide

Table I
M.C.G. Results

16 cases of open bladder neck		{ Incomplete milk-back—5 { Confirmed by cystoscopy—10 { Not confirmed—1
Remainder	Closed—3	{ Incomplete milk-back—2 { Stress incontinence—1
	Normal—1	
	Unable to void—1	

Table II
Cystoscopy

14 cases of open bladder neck	
Remainder	Low urethral pressure profile and
	B.N. open on M.C.G.—3
	Incomplete milk-back—2
	B.N. open on M.C.G.—2

Table III
Urethral Pressure Profile (19 only)

Low in 11	
Remainder—8	Incomplete milk-back—2
	B.N. open on M.C.G. and cystoscopy—1
	B.N. open on M.C.G. only—4
	B.N. open on cystoscopy only—1

Table IV
Treatment

I. Medical		Ave. time
Cetiprin—5	{ Improved—4 { No benefit—1	10 weeks
Tofranil—6	All improved	9½ weeks
Anal plug—6	{ Improved—3 { No benefit—3	10 weeks

II. Surgical

2 cases { Tofranil→Anal plug→Sling→Stimulator→No benefit
 { Bilateral re-implant and tightening of B.N. Improved after 4 months

Edwards clip—1. Improved.

1 case. No treatment. Review

bladder neck. The object of this investigation was to attempt to classify this group of 21 children in whom a wide bladder neck was the sole physical finding.

It is unlikely that this was only a congenital basis, as almost half the children had had a period of continence preceding their incontinence. The fact that conservative measures have been successful in the majority of cases suggests that control of the urethral sphincter may have been regained. It would be valuable but perhaps difficult to justify repeating these investigations on cured cases to see if the bladder neck has been altered in any way.

Equally interesting is the natural history of the condition. Are these children likely to retain some degree of weakness in their urethral mechanism so that following the trauma of childbirth they are more likely to develop stress incontinence in adult life? De Backer and Williams, in their account, have described 11 cases of wide bladder neck and note the association with spasm of the external urethral sphincter, demonstrated by a micturating cystogram. This could not be confirmed here by the micturating cystogram. The highest conscious urethral pressure profile was 88 cm and in this age-group this would not be indicative of spasm. Reference is made in the same article to the association of weakness of the vesico-ureteric junction resulting in reflux and the wide bladder neck. In this series only 1 case of reflux was found.

Taylor (1969) described 3 cases of incontinence and primary dilatation of the bladder neck and urethra in boys. Two had urinary tract infections and only diurnal incontinence and reflux and were treated conservatively. The third had reflux and nocturnal and diurnal incontinence and was treated by a ureteric re-implantation. All improved within 4 to 5 years and subsequent micturating cystograms on the first 2 showed no change. The author suggested widespread weakness of the bladder musculature and posterior urethra, but had no direct evidence for this.

The role of conservative treatment is difficult to assess. All successful measures in this series were effective on average after 10 weeks' trial, which indicates that treatment must be continued for at least this time. As the average age is between 9 and 10 years, the puberty growth spurt may have been responsible for some of this improvement. This further reinforces the case for conservative management. A long-term follow-up is necessary to determine if there is any relapse following discontinuation of drugs and appliances after a cure has been achieved. It is also difficult to assess the iatrogenic effect of a stay in hospital with the discomfort of some of the investigations and the possible threat of further investigations should treatment not produce continence.

Surgery should be reserved for the cases in whom the diagnosis is certain and who have failed to respond to the varied conservative measures over a reasonable period of time. If it is assumed that the wide bladder neck exists as an entity it would be reasonable to carry out a bladder neck tightening operation, either by an abdominal approach in a young girl or boy, or per vaginam in an older girl.

A prospective trial is needed with randomised treatment and controls to ascertain which of the conservative measures are more effective. In this type of problem it is difficult and not justified to withhold treatment, so it is impossible to assess the natural remission rate.

Conclusions

Diurnal incontinence in a young child is a significant symptom.

A wide bladder neck may be the only obvious cause.

Conservative measures carried out for at least 10 weeks may produce a cure in three-quarters of the cases.

Surgery may be necessary for resistant cases.

The children should be followed up on a long-term basis to establish the natural history of the disorder.

We should like to acknowledge the help and assistance from Dr T. Sherwood, Consultant Radiologist, Sister Fay and Mr K. Wallace, Technician, E.C.I. Department, Shaftesbury Hospital, in the preparation of this paper.

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The Treatment of Interstitial Cystitis by Cystolysis with Observations on Cystoplasty¹

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Interstitial cystitis, or “the elusive ulcer” as Hunner originally described it, is a well-recognised but fortunately not a particularly common condition (Hunner, 1914). The enigma of its aetiology and the many medical and surgical approaches that have been used in its treatment reflect the generally unsatisfactory state of affairs both for the patient and the urologist (Smith, 1952; Badenoch, 1971).

The clinical problem was well summarised by John Ormond of Michigan, who stated “it is characteristic of these patients that they have consulted many physicians, have received many diagnoses, have been treated in many ways, operative and otherwise, all without relief. Many have been relegated to the medical scrap-heap as neurotics” (Ormond, 1935).

There is a group of patients, almost always middle-aged females, who present with characteristic symptoms of frequency by day and by night, sensory urgency, suprapubic and perineal pain. The pain makes the patient feel that it would be relieved by voiding but usually it is not; there is marked frequency due to the discomfort of bladder distension and the urine is characteristically sterile.

The cystoscopic appearances may initially appear reasonably normal, but after quite mild distension under general anaesthesia discrete areas of increased vascularity and petechiae occur in the dome of the bladder, the urine becomes bloodstained and linear splits in the mucosa may be seen; an ulcer is however rare, and the trigone is characteristically spared and usually appears normal. A petechial reaction on bladder distension does not necessarily constitute interstitial cystitis but the diagnosis would be gravely suspect without it.

Temporary clinical improvement after bladder distension is usual and may be of some diagnostic help; the symptoms return within a few weeks but will repeatedly disappear after further distension although the bladder itself becomes progressively less distensible.

Histological changes show non-specific inflammation but every case should be biopsied, repeatedly if necessary, in order to exclude the symptomatic imitators tuberculosis, infiltrating carcinoma and schistosomiasis, etc. The diagnosis is essentially made on a time-proven basis.

Our urodynamic studies have shown that although “bladder spasms” are frequently referred to in the clinical description, the filling cystometrogram is characteristically normal in the majority of cases apart from the limitation of capacity. Figure 1 A shows the flat subtracted detrusor curve on the filling cystometrogram of a patient with interstitial cystitis in spite of a capacity of only 150 ml; this compares with the systolic neuropathic cystometrogram (Fig. 1 B) showing typical uninhibited detrusor contractions on filling.

Voiding cine cysto-urethrography shows that the bladder usually empties completely; vesico-ureteric reflux is not infrequently seen as a result of inflammatory change.

Many drugs have been advocated in the treatment: potassium iodide, warm boric acid, silver nitrate, dimethyl sulphoxide, chlorthalidone, butazolidin and steroids have been applied locally with varying results (Pool and Rivers, 1944; Johnston, 1956; Wishard *et al.*, 1957; Stewart *et al.*, 1972);

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steroids, antihistamines, heparin and oxy-phenylbutazone, etc., have been used systemically (Hoyt, 1952; Simmons, 1961; Weaver *et al.*, 1963; Guerrier *et al.*, 1965); there is perhaps a suspicious absence of sizeable and well-controlled series of patients treated with long-term systemic steroids and the complications of long-term medical or conservative management may sometimes exceed those of surgical treatment.

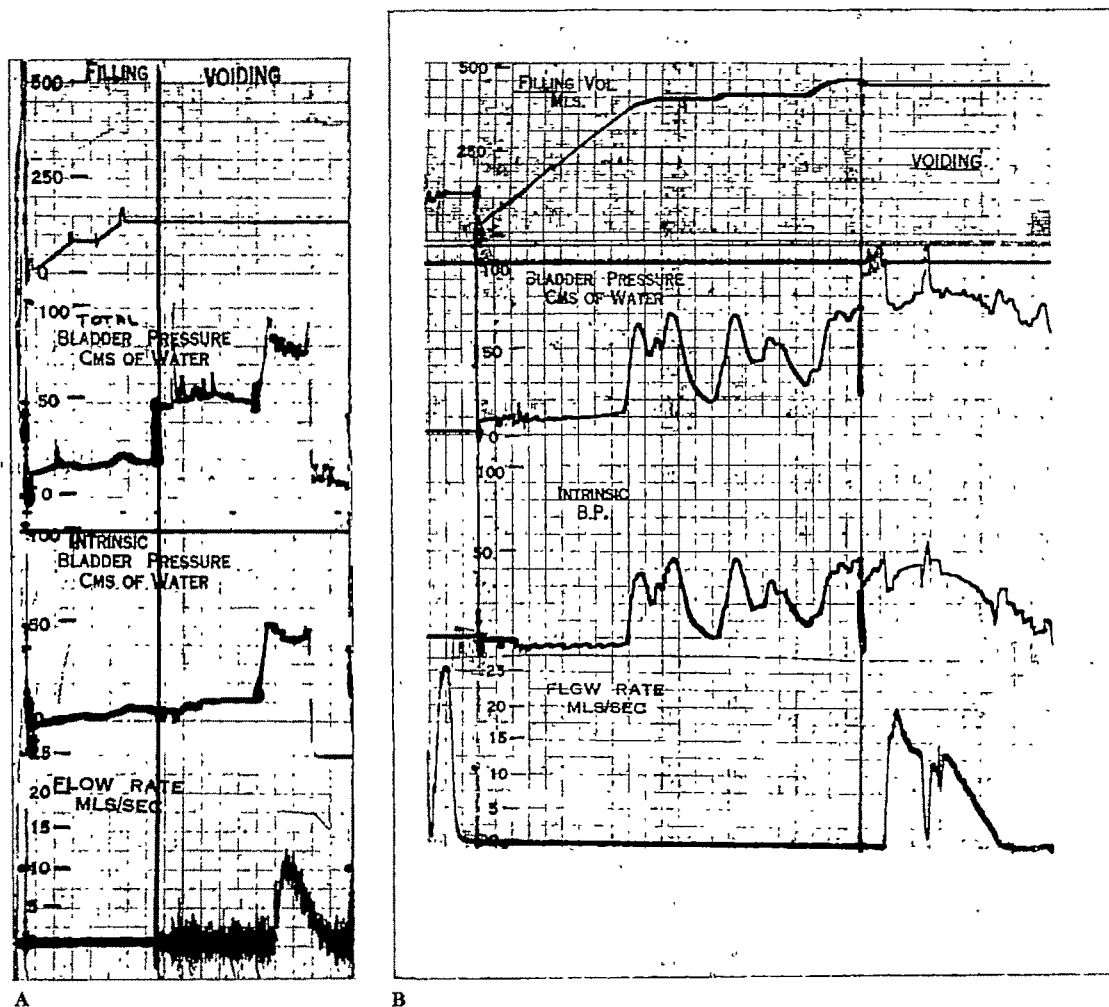


Fig. 1. Cystometrograms. (A) Filling and voiding studies in a patient with interstitial cystitis. Note flat subtracted detrusor curve on filling (intrinsic bladder pressure). (B) Filling and voiding studies in a patient with a systolic neuropathic bladder. Note the uninhibited detrusor contractions on filling.

Of the surgical approaches, repeated bladder distension under anaesthetic is probably the mainstay of treatment with or without endoscopic diathermy and local treatment. Partial cystectomy has occasionally proved successful but in general unreliable, and in view of our experience with cystolysis we suspect that good results are more likely to be due to sensory denervation produced by the incidental dissection rather than the resection itself, which must of necessity be inadequate. Urinary diversion is undertaken when all conservative medical and surgical approaches have failed.

We have been particularly interested in the treatment of this condition by local supratrigonal denervation and it is the purpose of this paper to describe the operation of cystolysis (Turner Warwick, 1971) and discuss its results in relation to those of cystoplasty which, in general, we have found to be satisfactory over a number of years.

The principle of cystolysis depends upon making a definitive diagnosis of interstitial cystitis at a time when the bladder can still be distended to a reasonably normal capacity under anaesthesia; we fully recognise, of course, that the diagnosis of interstitial cystitis must rest upon a time-proven basis but, at the time of initial presentation, patients with this condition usually have a normal bladder capacity. Provided with the possibility of treating the condition effectively, if not fundamentally, at this stage, it is usually not difficult to make a definitive diagnosis within about a year of presentation and bladder contraction should not have progressed significantly within this period of time.

The operation was conceived on the basis that the denervation should not compromise the sphincter mechanism nor the bladder base sensation necessary to convey patient awareness of the state of bladder distension. These may be compromised by division of major nerve trunks and we therefore tried the technique of cysto-cystoplasty, described to this Association in 1966 (Turner Warwick and Handley Ashken, 1967). In this technique the bladder is transected above the ureteric orifices, the upper part of it depending upon its blood supply from its superior vesical vessels; it is then resutured to the base of the bladder. Although this technique is reasonably successful it seems that a lesser procedure might give comparable results.

Cystolysis

The bladder is explored through a lower abdominal incision and freed from its surrounding tissues; superior vesical vessels are usually divided and the dissection is carried down to the trigone posteriorly, the ureteric sheath is left intact and the ascending branches of the inferior vesical vessels are divided down to the external surface of the bladder; this presumably divides most of the sensory pathways to the upper part of the bladder. We usually leave the patch of adherent peritoneum on the dome of the bladder intact and use this to elevate the dome of the bladder by suturing it to the posterior surface of the rectus muscle; this "anterior hitch" (Fig. 2) is done to prevent the bladder from contracting into the pelvis during the period of catheter drainage and risking incarceration in the healing process the elongated tube-shape of the bladder allows free expansion and detrusor evacuation and, when it is freely available, we usually wrap the omentum around it to retain its mobility. Although the operation is simple in principle, quite a large number of small vessels have to be divided and we have found the long diathermising scissors to be particularly helpful in this procedure.

We usually drain the bladder by a suprapubic catheter postoperatively; this enables one to be certain that the bladder is voiding efficiently before the patient leaves hospital without further investigation or manipulation.

The operation can justifiably be described to the patient as a simple procedure and the decision to offer its trial is mostly dependent upon the individual circumstances; the fact that the bladder base remains undisturbed does not compromise a subsequent cystoplasty if this becomes indicated.

Results

The results are summarised in the Table; all the patients in this series have lost their bladder pain, the majority were able to hold their urine for longer periods by day and had less frequent nocturia, partly as a result of the diminished bladder discomfort and partly as a result of an overall increase in the conscious bladder capacity. Somewhat surprisingly the endoscopic appearances usually show a return to normality, but the bladder capacity under general anaesthetic only increased in

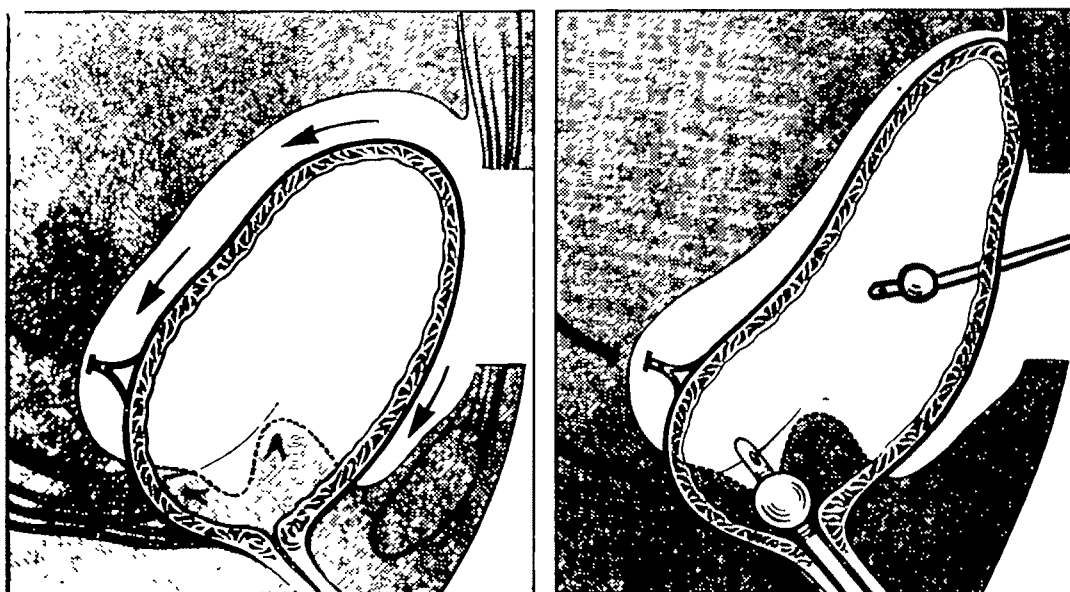


Fig. 2. Supra-trigonal cystolysis for sensory urgency. Interstitial cystitis. (Bladder distensible to normal capacity under anaesthesia.) This demonstrates the extent of dissection necessary. Note the draining catheters and the anterior hitch.

about half of the patients. In 2 cases the operation failed because the patient developed a small-capacity bladder and became incontinent; one of these had a good result from a cystoplasty, but the second ultimately required a diversion. An area of necrosis occurred in the dome of the bladder in one patient and an anterior urinary fistula developed but closed on catheter drainage. Preservation of the stripped superior vesical vessels might reduce the occasional ischaemic complications. Excessive basal mobilisation may reduce trigonal sensation and risk nocturnal incontinence.

Discussion

The improvement in patients' symptoms following inadvertent rupture of the bladder during distension is often quoted and we have recently seen a patient with a long-standing interstitial cystitis who developed a carcinoma of the dome of the bladder which was treated by partial cystectomy with subsequent loss of painful frequency; it seems likely that relief of pain in these cases is the result of incidental denervation. The neurosurgical approach to interstitial cystitis is not new, but most previous reports have discussed the management of the small contracted painful bladder. Pieri (1926, quoted by Learmonth, 1931) used a pre-sacral neurectomy which gave indifferent results. Nesbit in 1947 advocated antero-lateral chordotomy for refractory interstitial cystitis with intractable pain and had good results in 4 out of 4 cases. Milner and Garlick (1957) and Mason and his colleagues (1960) used selective sacral neurectomy of the third sacral root and claimed excellent results with the relief of pain and some increase in bladder capacity. Meirowsky (1969) suggested that this operation should be performed only if the bladder could be distended under a spinal anaesthetic and an S.3 block. Bohm and Franksson (1957) thought that the condition in the bladder was secondary to disease of the posterior nerve roots (sacral rhizopathy) and they succeeded in producing a cystoscopic appearance in monkeys similar to interstitial cystitis after inducing sacral rhizopathy: they advocated posterior sacral rhizotomy and operated on 8 cases with varying degrees of success, reducing pain and frequency but not increasing the capacity.

Table

The Results of Cystolysis in 11 Patients

	Pain Dysuria	Frequency		Volume voided	Capacity under G.A.
		Day hrs.	Night (times)		
L. P. Mar. '66	++ / No	$\frac{3}{4}$ / 1	3-5 / 2	100 / 100	100 / 200
M. Q. Apr. '67	++ / No	1 / 4	4-5 / 0	150 / 450	400 / 500
R. B. Jan. '68	++ / No	$\frac{3}{4}$ / 2	2 / 1	100 / 100	275 / 350
L. E. Nov. '68	++ / No	$1\frac{1}{2}$ / 3	4-5 / 2	120 / 400	300 / ?
I. H. Sept. '69	+ / No	1 / 1	5 / 4	100 / 100	450 / 220
B. A. Feb. '69	+ / No	1 / 3	5-6 / 2-3	150 / 350	450 / ?
L. P. Apr. '70	++ / No	$\frac{1}{2}$ / 2-3	6-7 / 2	100 / 300	350 /
M. C. May '70	+ / No	2 / 3-4	10 / 1-2	150 / 200	450 / 350
I. R. Nov. '71	+ / No	1 / 4	2 / 1	200 / 300	400 / 450
S. X. Jan. '72	++ / No	2 / 3	4-5 / 1-2	200 / 300	700 / 350

The preoperative and postoperative status in each column is separated by the oblique line.

The nearest description to local sensory denervation for interstitial cystitis is that by Learmonth (1931). He described a technique of denervation by cutting the pre-sacral nerve and branches of the hypogastric plexus around the terminal part of the ureter; he treated a variety of conditions but had some success in 3 out of 4 patients with interstitial cystitis, relieving the pain but not improving the capacity.

We would not advocate a denervation procedure for a patient with interstitial cystitis which has undergone secondary contracture to a point at which it cannot be distended to a useful capacity under anaesthetic; for such cases we would proceed to a cystoplasty.

The success of the treatment of interstitial cystitis by cystoplasty depends on adequate excision of the bladder down to within 1 cm of the trigone leaving a slightly larger margin around the ureteric orifices in order to avoid compromising the anti-reflux mechanism or the urethro-vesical junction. Excessive basal mobilisation risks a sensory nocturnal incontinence.

The success of cystoplasty in general depends upon the re-establishment of an efficient voiding mechanism postoperatively; we routinely check this by careful urodynamic studies proceeding to appropriate selective sphincterotomy when necessary; these are repeated until the bladder emptying is complete and in most cases the urine remains sterile without repeated medication. (Turner-Warwick, 1970)

Colocystoplasty was originally performed in Middlesex Hospital by Sir Eric Riches and Mr I. H. Griffiths, and we are very grateful to them for allowing us to review their series of 24 patients; only 2 of these have continuing pain and these have endoscopic evidence of interstitial cystitis in what remains of the bladder above the trigone. There was no operative mortality in this series. We have preferred the technique of caecocystoplasty (Turner-Warwick and Handley Ashken, 1967) and 16 of the patients in this series had interstitial cystitis; all of these lost their pain and have good voiding capacities of up to 500 ml; in 3 cases the operation failed because we were unable to establish a balance between satisfactory voiding and continence.

It is sometimes reported that the bladder "regenerates" after a cystoplasty. Not infrequently the margin of bladder base between the trigone and the cystoplasty seems to broaden, but the suture line between the bowel and the bladder remains sharply demarcated and this clearly cannot be regarded as regeneration but rather as a recovery of the bladder wall expansion and sometimes related, possibly, to the sensory denervation incidentally involved in the cystoplasty.

Conclusion

In conclusion it seems that cystolysis is an effective way of alleviating the bladder pain for patients with interstitial cystitis and that this relatively simple procedure can be used in selected cases when the bladder capacity is reasonable under anaesthetic. Patients with a contracted bladder are usually well pleased with the results of a properly conducted cystoplasty; the essentials of a satisfactory cystoplasty, basal sensation and intact sphincter mechanism, are preserved in interstitial cystitis and the possibility of resurrecting a lower urinary tract should always be considered even if it was abandoned to a urinary diversion many years previously.

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Recurrent Urinary Infections in Girls: Effects of Urethral Dilatation¹

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In 1963, Lyon and Smith noted that many girls with recurrent urinary infections appeared to have some difficulty in passing urine, as assessed by the sound of the urine striking a chamber-pot, which was recorded and studied. On examination they observed that many of these girls had tight urethras, as calibrated by a bougie. After some anatomical studies, Lyon and Tanagho (1965) suggested that the site of narrowing in the urethra was a ring of fibrous tissue just inside the external meatus, which they termed "distal urethral stenosis". It was observed that this ring of fibrous tissue usually calibrated with a bougie at 14-16F, and generally could be ruptured at about 24-26F. After a single dilatation to 30-32F, about 70 per cent of these girls were cured of their infections. Recently, Lyon and Marshall (1971) have reported results with 864 children, of whom 65 per cent of 283 with symptoms of cystitis and 52 per cent of 297 with symptoms of pyelonephritis were cured by a single dilatation; however, in the presence of significant reflux, only 30 per cent were cured. Many other studies from the U.S.A. have confirmed that from 65 to 90 per cent of these children show improvement after a single urethral dilatation or urethrotomy (Knappenberger, 1963; Weiss *et al.*, 1968; Brannan *et al.*, 1969; Klein *et al.*, 1970; Vermillion *et al.*, 1971).

Hinman (1966) and Halverstadt and Leadbetter (1968) have proposed a possible mechanism whereby this improvement might be achieved: perhaps when the proximal urethra becomes dilated above the "distal stenosis", the urine flow is turbulent during micturition, and bacteria in the distal urethra are washed back into the bladder. After dilatation, and in the normal urethra, laminar flow is achieved, and this rapidly washes the bacteria away. Although Lyon and Smith originally stated that there was no correlation between the urethral calibration and the appearance of the urethra on cysto-urethrography, the diagnosis of "distal urethral stenosis" has tended to be associated with a "spinning-top" or "carrot" urethra. Further support for this hypothesis was provided by Kedar (1968), who noted that both recurrent infection and reflux were more common in girls with "spinning-top" or type A, rather than narrow or type D urethras (Fig. 1). However, careful studies by Shopfner (1967, 1970), de Haas (1969) and by Clayton *et al.* (1966) have shown conclusively that the appearance of the urethra can vary from one extreme to the other in a single child in a single examination, and they all concluded that it was not possible to diagnose "distal urethral stenosis" radiologically.

Furthermore, Immergut *et al.* (1967) calibrated the urethras of 136 normal girls and compared them with 77 girls with recurrent urinary infections (Immergut and Wahman, 1968), and found that the mean urethral calibre for the children with recurrent urinary infections was actually slightly greater than in the normal, uninfected children in each age-group. Similarly, Graham *et al.* (1967) found no significant difference in calibration between infected and normal girls. Studies

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by Forbes *et al.* (1969) and by de Domenico (1969) have shown that simple meatotomy—in which the distal constricting ring was divided without simultaneous urethral dilatation—failed to produce good results. By contrast, Harvard (1970) obtained good results when meatoplasty was combined with dilatation. Recently the position has been further complicated by the observation by Tanagho and McCurry (1971) that any tube with an inner diameter of more than 10F should not of itself obstruct urine flow under the normal range of voiding pressures.

Thus, there appeared to be many unanswered questions concerning the place of urethral dilatation in the management of recurrent urinary infections in girls and the concept of “distal urethral stenosis” as a disease entity seemed open to doubt. In an attempt to elucidate these problems, we have conducted 2 further investigations. Firstly, the results of urethral dilatation were analysed retrospectively in 86 girls treated for recurrent urinary infection over a 5-year period. This was followed by a controlled prospective trial of urethral dilatation in 22 girls, in which the effects of dilatation were compared with cystoscopy alone. The results were assessed clinically, by measurement of the urethral pressure profile and by cystometry.

Retrospective Study

Between 1965 and 1970, 86 girls aged between 4 and 12 were treated by urethral dilatation for recurrent urinary infection. In all cases infection was confirmed bacteriologically on at least one occasion, and most girls had had repeated courses of antibiotics before being referred. Preliminary investigation included bacteriological examination of urine, intravenous pyelogram and micturating cystogram. The intravenous pyelogram was normal in 68 and duplex in 7; in 7 cases there was some evidence of pyelonephritic scarring; 2 showed obstructive megaureter, and there was 1 case each of horseshoe kidney and crossed ectopia.

These cases were grouped according to the results of the micturating cystogram:

Group I (51 cases). No vesico-ureteric reflux.

Group II (19 cases). “Partial” reflux, but not reaching the kidney.

Group III (16 cases). “Complete” reflux, reaching the kidney.

The micturating cysto-urethrograms were also examined for the presence or absence of residual urine, and the urethral silhouette was classified according to Kedar (1968) (Fig. 1).

Under general anaesthesia, the urethral calibre was measured with a bougie; after cystoscopy, the urethra was dilated to between 24 and 32F, and in some cases external meatotomy was also performed. This was followed by continuous low-dose chemotherapy, using either sulphafurazole, nitrofurantoin or nalidixic acid for 3 to 6 months. Antibiotics were then stopped and the subsequent clinical course was observed. Results were graded as:

Cured. No clinical or bacteriological urinary infections for at least 1 year, having stopped all chemotherapy.

Better. Infections less frequent, or still receiving antibiotic therapy, or follow-up less than 1 year.

Unchanged or Worse.

Results

The clinical results, grouped according to the findings on micturating cystogram, are shown in Table I. 69 per cent of girls with no reflux (group I) and 63 per cent of girls with partial reflux (group II) were improved after dilatation, but only 28 per cent and 37 per cent were graded as cured. About one-third of these girls showed no improvement, and none was made worse. The results were much poorer when reflux was complete (group III) when 52 per cent of girls showed no improvement; many of these girls subsequently underwent re-implantation of ureters.

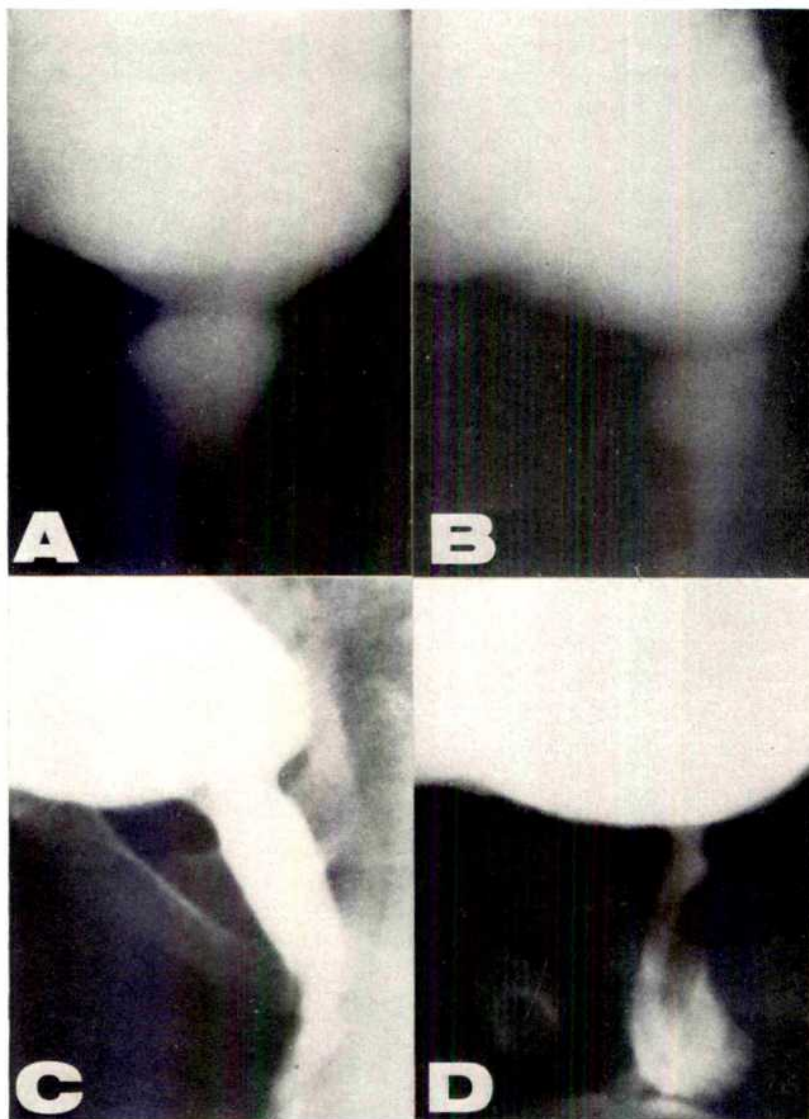


Fig. 1. Urethral silhouettes on micturating cysto-urethrography (after Kedar, 1968): types A and B—"Spinning-top" deformity, involving more (A) or less (B) than half the length of the urethra; type C—tapering; and type D—tube shaped.

The results of the 70 cases in groups I and II were taken together for further analysis, and those in group III were excluded.

The results in group I and II cases related to continence are shown in Table II. The results appeared to be less good in cases where there was a significant degree of day wetting.

The results in these cases related to residual urine are shown in Table III. There did not appear to be any relationship between the presence of some residual urine on the post-micturition X-ray film and the results of dilatation.

Table I

Retrospective Study. Overall clinical results of urethral dilatation in 86 cases, related to degree of vesico-ureteric reflux

Group	Cured	Better	Unchanged	Worse
I. No reflux (51 cases)	28%	41%	31%	0
II. Partial reflux (19 cases)	37%	26%	37%	0
III. Complete reflux (16 cases)	6%	37%	57%	0

Table II

Retrospective Study. Clinical results in 70 cases with little or no reflux related to continence

Continence	Cured	Better	Unchanged
Dry (40 cases)	40%	28%	32%
Wet—at night (30 cases)	17%	50%	33%
Wet—day and night (17 cases)	12%	41%	47%

Table III

Retrospective Study. Clinical results in 46 cases with little or no reflux related to presence or absence of residual urine on post-micturition X-ray film

Residual urine	Cured	Better	Unchanged
None (18 cases)	28%	39%	33%
Some (28 cases)	25%	32%	43%

The results in those cases related to urethral silhouette on micturating cysto-urethrography (Fig. 1) are shown in Table IV. Analysis failed to reveal a preponderance of any particular shape of urethra amongst girls who were improved by dilatation.

The results in those cases related to urethral calibration are shown in Table V. There was no significant difference between the results obtained in girls with urethras that were classified as tight (calibrated less than 16F) as compared to the remainder.

Table IV

Retrospective Study. Clinical results in 47 cases with little or no reflux related to urethral silhouette on micturating cysto-urethrography (after Kedar, 1968)

Urethral silhouette	Cured	Better	Unchanged
A (9 cases)	33%	22%	45%
B (14 cases)	21%	36%	43%
C (15 cases)	33%	40%	27%
D (9 cases)	11%	56%	33%

Table V

Retrospective Study. Clinical results in 53 cases with little or no reflux, related to urethral calibre

Urethral calibre	Cured	Better	Unchanged
Up to 16F (20 cases)	35%	25%	40%
More than 16F (33 cases)	30%	37%	33%

The results were also analysed in relation to several other factors, including the presence or absence of trabeculation on cystoscopy, the amount of dilatation performed, the addition of meotomy and the effects of repeated dilatation, but no significant correlation was found.

In view of the difficulty in predicting which girls would be improved by dilatation, and since the reasons why dilatations helped these girls remained quite obscure, a prospective controlled trial was undertaken.

Prospective Controlled Trial

22 girls aged between 6 and 12 were treated for recurrent urinary infection. Alternate cases underwent urethral dilatation to 32F (group I) under general anaesthetic, while the remainder were examined with the 12F child's cystoscope only (group II). Average age was 8.5 years in group I, and 7.9 years in group II. Intravenous pyelogram was normal in 21 cases and duplex in 1. Micturating cystogram showed no reflux in 19 cases, and partial reflux (not reaching kidney level) in 3 cases.

Bladder and urethral pressures were measured in the conscious child before and 3 months after treatment, and were also measured under general anaesthetic before and immediately after cystoscopy, with or without urethral dilatation. The urethral pressure profile was measured by the method described by Brown and Wickham (1969), as modified by Harrison and Constable (1970). Cystometry was performed by filling the bladder at 25 ml/min. Anal sphincter electromyography was performed with a bipolar anal plug electrode.

After examination under anaesthetic, all patients received sulphafurazole 0.5 g twice daily for 2 months; they were re-assessed with pressure measurements after 3 months, and their clinical state was regularly reviewed thereafter. At present, the girls have been followed for between 4 and 9 months.

Results

Preliminary clinical results (Table VI) were assessed by the same criteria as those used in the retrospective study. Since no girls have been followed for more than 1 year, none was graded as cured. So far, there appears to be no difference between the 2 groups: the same proportion of girls have shown improvement irrespective of whether the urethra was dilated or not.

Table VI

Prospective Controlled Trial. Preliminary clinical results in 22 cases

	Better	Unchanged	Worse
Group I (dilated)	7	5	0
Group II (not dilated)	6	4	0

Table VII

Prospective Controlled Trial. Mean peak urethral pressure results in cm water (with standard deviations) measured conscious before and 3 months after treatment, and under general anaesthetic

	Mean Peak Urethral Pressure (cm water)		
	Before treatment (conscious)	Under general anaesthetic	3 months after treatment (conscious)
Group I (dilated)	103±27	44±18	84±26
Group II (not dilated)	104±20	62±23	82±21

Urethral Pressure Profile. Mean peak urethral pressure results (with standard deviations)—conscious, before and 3 months after treatment (Fig. 2), and under general anaesthesia (Fig. 3)—are shown in Table VII. In all cases, the peak urethral pressure dropped significantly under general anaesthesia (by *t* testing, $P < 0.01$). The peak urethral pressure under general anaesthesia

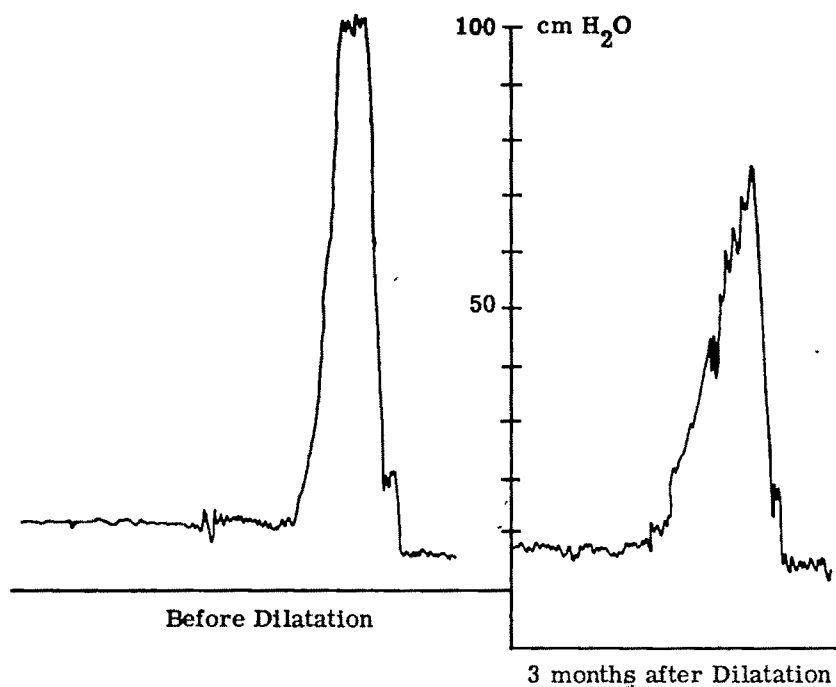


Fig. 2. Conscious urethral pressure profiles, measured before and 3 months after urethral dilatation; the peak urethral pressure is slightly lower after treatment.

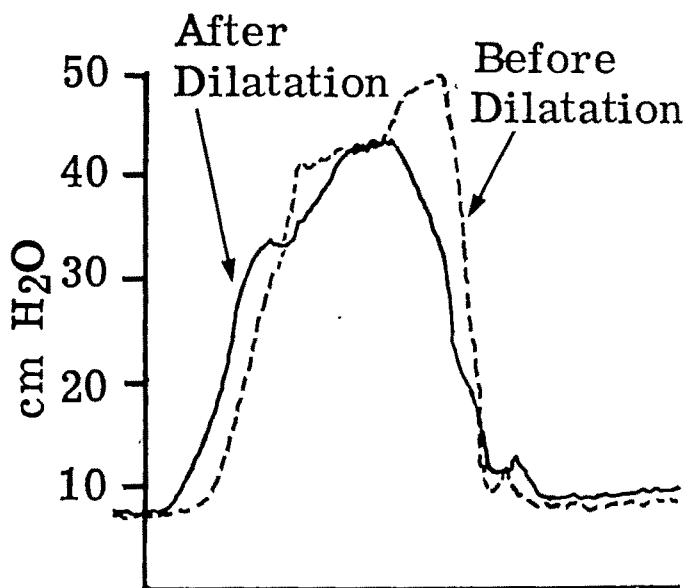


Fig. 3. Urethral pressure profile under general anaesthesia, measured immediately before and after urethral dilatation; the shape of the profile is altered, but the peak urethral pressure is unchanged.

did not alter after dilatation, although the shape changed in some cases (Fig. 3). Three months later, the conscious peak urethral pressure was slightly lower than before treatment, but there was no difference between cases that had had urethral dilatation (group I) and those who had only undergone cystoscopy (group II).

Table VIII

Prospective Controlled Trial. Mean peak urethral pressure results in cm water before treatment (with standard deviations) related to clinical response

	Mean Peak Urethral Pressure (cm water)	
	Better	Unchanged
Group I (dilated)	112±32	91±12
Group II (not dilated)	106±25	101±12

Further analysis (Table VIII) showed that the girls in group I (dilated) who improved had higher initial conscious peak urethral pressures than those who did not show improvement, and this difference was not seen in group II (not dilated). However, this difference was not statistically significant.

Cystometrogram. The cystometrograms fell into one of two patterns (Fig. 4). In 14 girls, a slow steady increase in pressure terminated in a sharp rise that accompanied the strong desire to void

Table IX

Prospective Controlled Trial. Mean pressure rise in centimetres water (with standard deviations) on filling cystometrogram related to clinical response

	Mean Pressure Rise (cm water) on Cystometrogram	
	Better	Unchanged
Group I (dilated)	34±17	19±3
Group II (not dilated)	19±14	19±2

when the bladder was full. However, in 8 girls the cystometrogram showed clear evidence of uninhibited bladder contractions, with frequent sharp pressure spikes which were associated with a transient desire to pass urine. The latter type of tracing was seen in 6 of the 7 girls who showed improvement after dilatation, and was associated with a clinical history of urgency of micturition and occasional damping of the pants by day which was usually attributed to an inability to reach the toilet in time.

The cystometrogram tracings were analysed by groups and clinical response. The mean pressure rise (with standard deviations) on the filling cystometrogram (Table IX) was higher in the girls in group I (dilated) who showed improvement, as compared to those that were clinically unchanged,

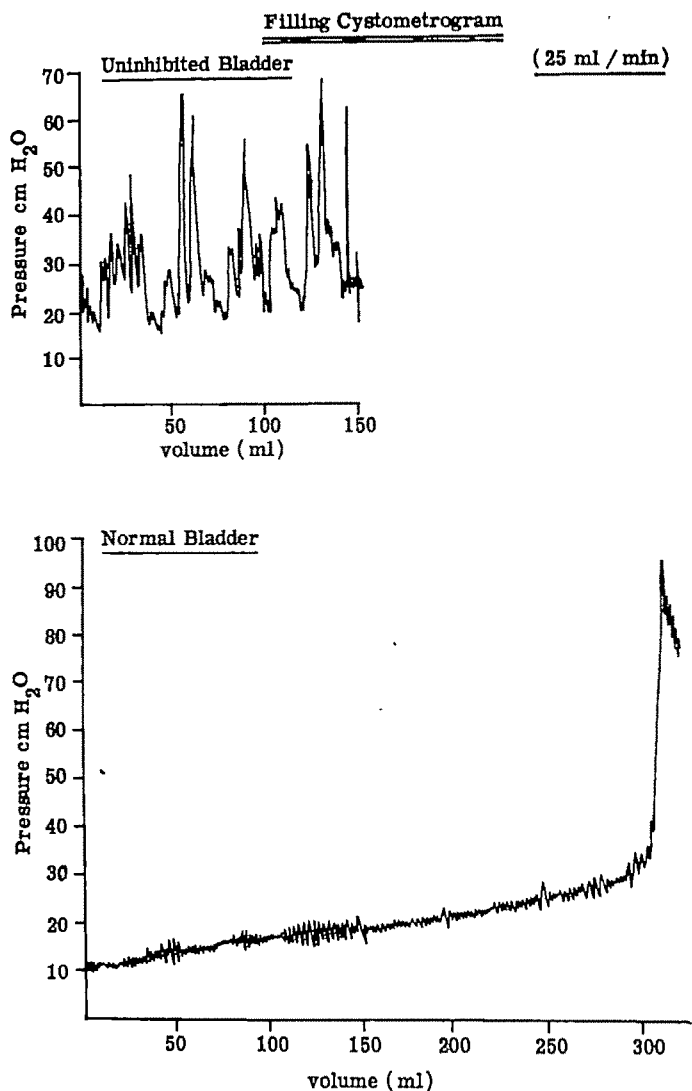


Fig. 4. Filling cystometrograms: the upper tracing shows a typical uninhibited bladder; the lower tracing is normal.

and this difference was not seen in group II (not dilated). However, this difference was not statistically significant. The mean bladder capacity (Table X) was significantly smaller in those girls in group I who showed improvement after dilatation as compared to those who were not improved (by *t* testing $P < 0.05$) and this difference was not seen in group II (not dilated).

Anal Sphincter Electromyogram. This investigation was normal in all 22 girls.

Discussion

The results of the retrospective study confirmed that about 65 per cent of girls with no serious vesico-ureteric reflux showed some improvement in their recurrent urinary infections when treated

Table X

Prospective Controlled Trial. Mean bladder capacity in millilitres (with standard deviations) on filling cystometrogram related to clinical response

	Mean Bladder Capacity (ml) on Cystometrogram	
	Better	Unchanged
Group I (dilated)	192± 68	304± 102
Group II (not dilated)	171± 42	163± 92

with a single urethral dilatation together with long-term antibiotic therapy. However, the results were unpredictable: the symptoms, the presence of residual urine, the urethral silhouette on cystourethrography, urethral calibration and cystoscopy gave no indication which girls would be improved by the urethral dilatation. The degree of dilatation and the addition of meatotomy appeared to be unimportant, and there was no evidence that repeated dilatation was any more effective than one single dilatation.

The prospective controlled trial showed little difference in the preliminary clinical results between the girls who had urethral dilatation and those who only underwent cystoscopy, and the urethral pressure profile results, before and after treatment, were virtually identical in dilated and non-dilated cases. However, there was a highly significant drop in urethral pressure after induction of general anaesthesia, and this is quite different from observations in adult women, where this effect is not seen (Donker *et al.*, 1972). This suggests that the external striated muscle sphincter is highly active in children, and it is of interest that the girls who showed improvement after dilatation were those who tended to have high urethral pressures, high bladder pressures and low bladder capacities. This agrees with the findings of Tanagho *et al.* (1971), who attributed the high urethral pressure to reflex spasm of the striated external sphincter, which was corrected by urethral dilatation; they suggested that the spasm was induced by "sensitisation of the distal urethral ring".

Lapides and Diokno (1970) have shown that persistence of the uninhibited "infant type" bladder is very common in girls with recurrent urinary infection. The finding of this type of bladder in 6 of the 7 girls who were improved by dilatation in this study is of particular interest, and suggests that uninhibited bladder may frequently be associated with abnormality of the external striated muscle sphincter. Such a "dysfunctional bladder syndrome" (Fig. 5) may be a cause of recurrent urinary infection in girls, due to an abnormal tendency of the external sphincter to contract inappropriately during micturition, thus interfering with bladder emptying. Once infection occurred, bladder and sphincter irritability would increase, and together with local irritation and vulvitis might produce a vicious circle. It is possible that forcible dilatation of the external urethral sphincter might temporarily relax the sphincter, and break the vicious circle, in much the same way as anal dilatation may help patients with anal fissure.

Marshall (1971) has noted how difficult it may be to choose the best therapeutic programme in the treatment of girls with persistent and recurrent urinary tract infection, associated with no anatomical abnormality. It may be suggested that the urethral pressure profile and cystometrogram may offer assistance in choosing the best therapeutic regime in each particular case. The presence of a high urethral pressure profile with an uninhibited cystometrogram would seem to be a strong indication for urethral dilatation; if symptoms persist, and particularly if day wetting is a problem, then the addition of anticholinergic drug therapy may be of value. If the cystometro-

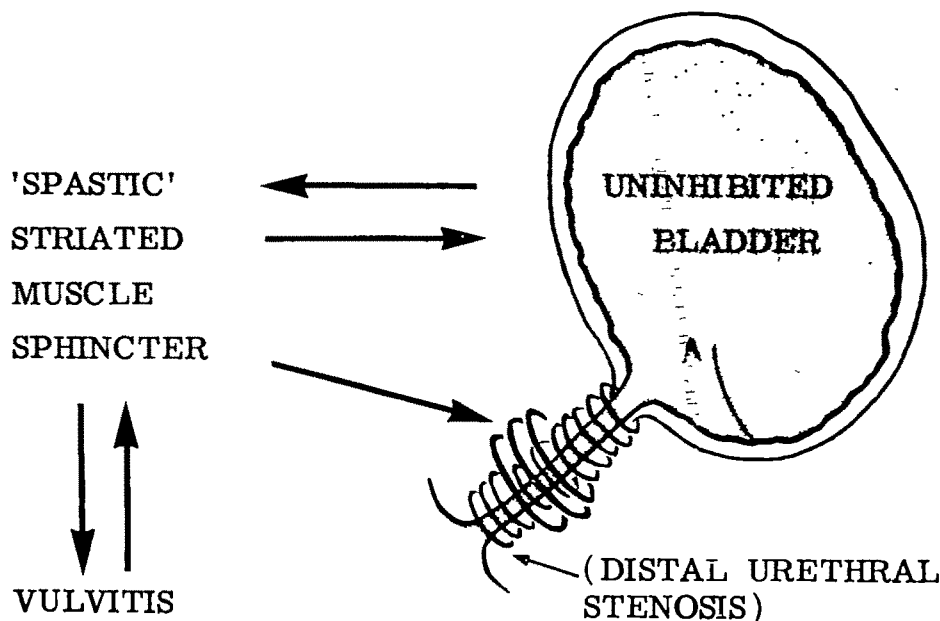


Fig. 5. "Dysfunctional bladder syndrome." Uninhibited bladder may frequently be associated with spasm and inappropriate contraction of the external sphincter; urinary infection and vulvitis increase the bladder irritability, causing a vicious circle. Urethral dilatation may be helpful in these cases, together with anti-cholinergic drug therapy if day wetting is a problem.

gram is normal, then treatment should probably be directed towards careful vulval hygiene, time training and adequate long-term antibiotic therapy (Stansfeld, 1966).

In either case it would seem advisable to perform anal sphincter electromyography in order to exclude significant neurogenic abnormality (Dorfman *et al.*, 1969; Martin *et al.*, 1971), particularly since an increased incidence of spina bifida occulta has been reported in these patients (Manley and Frech, 1970).

Summary

The effects of urethral dilatation have been investigated in girls with recurrent urinary infection. About 65 per cent of girls showed some improvement when this procedure was combined with long-term antibiotic therapy, provided that there was no serious vesico-ureteric reflux. However, the results were unpredictable, and in a controlled prospective trial the preliminary results of dilatation did not differ significantly from those obtained with cystoscopy alone. Nevertheless, improvement after dilatation did seem to be associated with a high urethral pressure profile, high bladder pressure, small bladder capacity and marked detrusor irritability; it is suggested that this "dysfunctional bladder syndrome" may be the cause of recurrent infections in these cases, and that improvement may be anticipated after urethral dilatation, which should be combined with anti-cholinergic drug therapy if day wetting is a co-existing problem.

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The Management of Superficial Bladder Tumours with Intravesical Epodyl¹

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Rapidly recurring tumours which are multifocal, superficial and confined to the bladder urothelium can present problems in management. In some patients the neoplastic change is so widespread that repeated diathermy or resection is not sufficient. If the disease is extensive in the urethra cysto-urethrectomy is the wisest procedure; this does seem however a high price to pay for a lesion which has a relatively benign course. If the disease is confined to the bladder, other forms of less radical therapy may be employed. Of these, intracavity chemotherapy is probably the most successful. Various workers have published results using thiotepe (Jones and Swinney, 1961; Veenema *et al.*, 1962, 1969; Esquivel *et al.*, 1965; Abbassian and Wallace, 1966; Mitchell, 1971). Recently a preliminary series using intracavity Epodyl, triethylene glycol di-glyceridyl ether (I.C.I.) was published (Riddle and Wallace, 1971).

The purpose of this communication is to show the results in 64 patients with superficial tumours treated with intracavitary Epodyl. 44 of these patients have been followed for a year on prophylactic treatment with Epodyl and 32 for 2 years.

The treatment regime has been described elsewhere (Riddle and Wallace, 1971), but now has two changes, firstly if the response is poor a 2 per cent solution may be used, and secondly exfoliative cytology has been discontinued as it was found to contribute nothing to the follow-up of these patients. Epodyl is now marketed in 1 ml ampoules which makes occasional treatments less expensive and also reduces the risk of overdosage.

Treatment, once started, is continued indefinitely provided the response is satisfactory, at monthly intervals for a year and then, if the bladder is clear, at 2-monthly intervals for a further year. If there is no recurrence with this regime it is prolonged to 3-monthly instillations coinciding with cystoscopic attendances.

Results

64 patients have now been treated at one central clinic. For the purpose of this paper patients referred for treatment from other hospitals are not included as adequate follow-up of these patients has proved impossible. I.U.C.C. pathological grading is used and is shown in Table I. It is disturbing how many patients escaped histological classification altogether. If it is assumed that the available distribution is correct, then approximately 74 per cent will be in the P.i.s. group. The number of patients with P.1a and P.1b lesions is small and this often refers to their original histology, which may have been some years before treatment with Epodyl started. Conclusions as to the efficiency of the drug in each group cannot yet be drawn.

The length of previous history of bladder tumour ranged from 1 to 28 years with an average of 6. It does illustrate the unchanging nature of the pathology in most patients.

The results are assessed endoscopically in 3 groups:

Group A. No demonstrable tumour within the bladder.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

Group B. Improvement in the state of the bladder when compared with before treatment (as little as one minute recurrence would place a patient in this group as opposed to group A).

Group C. Failure of treatment.

Small recurrences are burnt or left alone; if the former, then no Epodyl treatment should be given for at least 3 weeks as a strong local reaction may ensue.

Table I

Histological Classification in 64 Patients

(Biopsy Results)

P.i.s.	34
P.1a	5
P.1b	7
Unclassified	18

Table II

Three-month Follow-up

No. of Patients	A	B	C
64	38	24	2
100%	59%	38%	3%

The percentage is taken to the nearest whole figure.

Table III

Six-month Follow-up

No. of Patients	A	B	C
56	30	19	7
100%	54%	34%	13%

Tables II, III, IV, V and VI show the 3-month, 6-month, 1-, 2- and 3-year follow-up results, respectively. The percentage in group B is greater in the earlier results. There is then a gradual polarisation into groups A and C, mainly into the latter. Although the numbers are insignificantly small at 3 years, there are at present no patients in category B. At the 2- and 3-year follow-up periods the figures are altered by 3 patients who died of causes other than their bladder cancer. They were free from bladder disease at death and had they been alive would have been in group A. The corrected figures are in brackets.

These figures indicate that the majority of patients whose treatment was initially successful remained satisfactory and as time passes the fallout is amongst those patients who showed a partial response (group B). Only long-term follow-up will prove this point. Only 1 of the 11

failures at 2 years has been treated with diathermy: 5 have undergone cystourethrectomy, 2 radiotherapy, and the remainder have died from other causes.

These further long-term results using Epodyl both as a treatment and a prophylaxis on a long-term basis appear to substantiate the results of the preliminary series. The results are more

Table IV
One-year Follow-up

No. of Patients	A	B	C
44	28	6	10
100%	64%	14%	23%

Table V
Two-year Follow-up

No. of Patients	A	B	C
32	15	6	11
100%	47%	19%	34%
	corrected (56%)		

Table VI
Three-year Follow-up

No. of Patients	A	B	C
8	4	...	4
100%	50%	...	50%
	corrected (63%)		

favourable than those with Thiotepa, and Epodyl carries none of the systemic side-effects of Thiotepa. For these reasons Epodyl is a useful drug in certain patients when conventional endoscopic methods appear to be failing.

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Carcinoembryonic Antigen and Urothelial Carcinoma¹

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Carcinoembryonic antigen (CEA) is a glycoprotein whose molecular weight is 200,000 that has been localised on the plasma membrane of some tumour cells (reviewed by Laurence and Neville, 1972).

It was originally described by Gold and Freedman (1965) and so named because it was isolated from malignant tumours of the colon, endodermal tissues of foetuses between 2 and 7 months and detected by immunological methods against antisera raised in heterologous hosts.

Thomson *et al.* (1969) extended Gold's observation by finding CEA in the plasma of patients with gastro-intestinal carcinoma, as a result of which he suggested a radioimmunoassay for the clinical detection of CEA.

The principle of this method is simple and very sensitive. A known quantity of CEA prepared from colonic tumours and labelled with ¹²⁵I is added to a known quantity of goat anti-CEA serum and the sample to be tested. If no CEA is present in the sample, the labelled CEA will bind with the goat anti-CEA which is then precipitated with horse anti-goat serum. The amount of bound iodine in the precipitate is then measured. If CEA is present in the sample, some of the labelled CEA will be displaced from the precipitate. By comparison with a standard curve, the amount of CEA in the specimen is calculated. Less than 1 ml of plasma or urine is required for the test, which takes 2 days to complete.

During the past 3 years, further experience using similar or modified methods has shown that raised CEA levels can occur in the plasma of patients with a variety of malignant tumours other than those of the gastro-intestinal tract, including carcinoma of the bladder and in some non-malignant disorders (Laurence and Neville, 1972).

We wish to report the findings of CEA in the urine of patients with urothelial carcinoma in relation to:

1. The incidence of CEA in the urine of normal adults.
2. The results of our investigation of patients with urothelial carcinoma.
3. The possible clinical relevance of our findings.

1. The Urine of Healthy Adults

Examination of random urine samples from 46 healthy men aged 16-90 years showed a small amount of CEA in every subject save one (Table I). The mean level was 14 ng/ml and statistical analysis suggested that the upper limit of normal be 35 ng/ml. Four men had levels higher than this but none had evidence of urinary disease. There was no variation with age nor was there any regular diurnal variation. Urine may be left at room temperature for 3 days without affecting the result, and subsequent tests have shown that neither haematuria, proteinuria nor glycosuria influence the CEA level.

Results from 48 healthy female controls showed greater variation, giving a mean of 47 ng/ml

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

and an upper limit of normal of 110 ng/ml. No special precautions were observed when collecting the urine; mid-stream specimens were not used. Therefore, it was considered that the higher results obtained in women might be due to 2 possible causes:

1. Bacterial contamination
2. Contamination with vaginal or cervical secretion

either or both of which might possibly influence the amount of CEA or CEA-like material.

Table I

Urinary CEA Levels in Healthy Subjects and in Association with a Variety of Disorders

Disorder	MALES					FEMALES				
	Urinary CEA ng/ml				Incidence of Positive Assays ¹	Urinary CEA ng/ml				Incidence of Positive Assays ¹
	< 35	35-60	61-100	> 100		< 35	35-60	61-110	> 110	
Normal controls	42	3	1	1	4/46	30	8	4	6	6/48
Carcinoma of bladder	16	5	6	20	31/47	2	2	...	9	9/13
Previous carcinoma of bladder ²	32	1	...	1	2/34	9	1	...	...	0/10
Carcinoma of bladder plus infection	2	2	..	13	15/17	...	...	...	3	3/3
Non-urothelial malignant tumours	16	...	...	...	0/16	5	3	1	2	2/11
Benign disease	6	1	...	..	1/7	3	...	1	1	1/5
Urinary infection	...	...	...	5	5/5	...	1	...	3	3/4

¹ Upper limit of normal in males is taken as 35 ng/ml and in females as 110 ng/ml for random urine specimens (Hall *et al.*, 1972).

² No clinical evidence of recurrent tumour.

Table II

Urinary CEA in Women according to Method of Urine Collection

Type of Specimen	Urinary CEA (ng/ml)			
	< 35	35-60	61-110	> 110
Random	30	8	4	6
Mid-stream	39	9	2	...
Catheter	7	...	...	...

All urine samples had been tested for bacterial content by means of dip inoculum plates so that we were able to analyse the CEA levels according to their degree of bacterial contamination. It was found that bacteria, irrespective of their number or identity, did not influence the measured level of urinary CEA.

Examination of vaginal secretions from 6 healthy women showed very high levels of apparent CEA and this is thought to be the reason for the higher results in females. It is also probable that prostatic fluid contains similar mucoproteins, which may explain the small group of raised levels seen in men.

As a result, mid-stream specimens have been used subsequently with elimination of the very high "false positive" results (Table II). Catheter specimens all contained less than 35 ng/ml, but these cannot be used routinely and it is anticipated that the future use of M.S.U.s with occlusion of the vaginal introitus with a plug of cotton-wool will prove satisfactory.

2. Urinary CEA and Urothelial Carcinoma

Males (Table I). Analysis of urinary CEA levels in 47 men with proven transitional cell carcinoma of the bladder or posterior urethra shows that 31/47 had levels in excess of 35 ng/ml. Of 34 men who had had transitional cell carcinoma in the past but at the time of investigation were cystoscopically and cytologically tumour-free, all but 2 fell within the normal range.

Table III

Urinary CEA Levels in Male Patients as a Function of the Stage and Grade of Transitional Cell Carcinomas

	Urinary CEA ng/ml			
	< 35	35-60	61-100	> 100
<i>Stage</i> ¹				
T1	9	1	0	4
T2	1	...	...	2
T3	5	3	6	6
T4	2	1	1	7
<i>Grade</i>				
Well differentiated	2	...	...	2
Moderately well differentiated	3	1	2	8
Poorly differentiated	6	3	4	5

¹ UICC classification.

Similarly, urine from all 16 men with non-urothelial carcinomas was normal. These included 3 men with carcinoma of prostate and 4 with renal cell carcinoma.

Six of 7 with benign disorders also were within the normal range, but 5 men with symptomatic urinary tract infection had raised levels of the same order as those given by carcinoma of the bladder.

We know that bacteria themselves do not contribute to urinary CEA so we conclude that inflammation of transitional epithelium as well as malignant change causes the release or production of CEA or CEA-like material.

Urine collected from ileal conduits contains large quantities of apparent CEA. This is not surprising, for the normal intestinal mucosa contains CEA. If urine is collected simultaneously from the ureters and the ileal stoma, the CEA content of ureteric urine is normal while that of the stoma urine is raised.

The occurrence of elevated urinary CEA levels in men with transitional cell carcinoma compared with all other groups, except urinary infection, is highly significant.

The group included several patients whose tumours were present only in prostatic ducts or posterior urethra, and in addition to the results shown, 1 man with a solitary tumour of the ur ter had a raised urinary level.

Analysis of results according to clinical stage (Table III) shows that higher CEA levels tend to occur in association with more invasive tumours. However, over one-third of stage T1 tumours gave raised levels, some of them over 500 ng/ml. Four of 7 with *in situ* disease only had CEA levels higher than 200 ng/ml.

When considering the degree of differentiation of the tumours this factor did not appear to influence the CEA level (Table III).

Females. The number of women with carcinoma of the bladder was smaller but the same basic trend was observed (Table I). Nine of 13 with proven bladder tumours had CEA levels above normal, 4 of the 9 having T1 tumours only. None who were tumour-free as determined by cystoscopy at follow-up had raised levels.

Of the women with other malignancy, 2 gave positive results. One had carcinoma of the cervix and the other malignant lymphoma that involved both kidneys.

Three of 4 with cystitis also had positive results.

Plasma CEA. Results are shown in Table IV. The normal range for plasma CEA is up to 12.5 ng/ml on the basis of which 31/73 patients with proven tumour had raised levels. Comparison of plasma

Table IV

Plasma CEA Levels in Patients with Bladder Carcinoma

Bladder Carcinoma	Plasma CEA ng/ml			Incidence of Positive Assays
	< 12.5 ¹	12.5-40	> 40	
Local Disease	42	29	2	31/73
Metastases Present	2	5	6	11/13

¹ 12.5 is taken as the upper limit of normal (Laurence *et al.*, 1972).

CEA with urinary results in the same patient failed to show any consistent correlation. This suggests that CEA present in the urine is a product of the urothelium and not removed from the blood by the kidneys. This is endorsed by many of the patients with other tumours who had very high plasma levels but normal CEA in the urine.

Recent experience indicates that the threshold of 12.5 ng/ml may be too low and only the 2 results above 40 ng/ml are considered diagnostic, both of these being patients with deeply invasive tumours.

However, in patients with metastases, the plasma results were more consistently raised. 11 of 13 had abnormal levels, of which 6 were of diagnostic level.

The incidence of positive plasma results is not as high as that found with carcinoma of the colon, bronchus or breast (Laurence *et al.*, 1972).

From these results it is evident that measurement of CEA in the urine will detect 66 per cent of cases with transitional cell carcinoma of the urothelium. Measurement of plasma CEA detects very few tumours with certainty.

3. Clinical Relevance of Urinary CEA

Having demonstrated the presence of high levels of CEA or CEA-like substances in the urine of patients with urothelial carcinoma, it is now important to determine the clinical value of our observations.

It has been suggested that measurement of plasma CEA might be used to assist the early detection of gastro-intestinal carcinoma and it was with this end in view that the radioimmunoassay was developed. Results have proved disappointing, however, in that conclusively diagnostic plasma results occur in only a small proportion of early tumours and in this respect our experience of transitional cell carcinoma is no exception.

Measurement of urinary CEA, on the other hand, appears more promising. A positive detection rate of almost 70 per cent compares very favourably with the cytological examination of urine. For the urinary CEA assay, 2 ml of a mid-stream specimen of urine is all that is required. As there is no deterioration with time or bacterial contamination, urine may be sent through the post without preservative and it is suggested that this might provide an alternative to urinary cytology for industrial screening.

In hospital practice, it could provide a useful aid alongside cytology and cystoscopy in the primary diagnosis and routine follow-up of patients with urothelial tumours. The presence of an elevated urinary CEA level in the absence of urinary infection and ileal conduit or uretero-colic diversion is strongly suggestive of transitional cell carcinoma somewhere in the urinary tract.

Examination of ileal conduit urine after cystectomy is of no value, but as significant elevation of plasma CEA occurs in deeply invasive or metastatic disease, the persistence of a positive plasma assay or a rising plasma titre after cystectomy is suggestive of extravesical spread.

Summary

1. CEA or CEA-like substances are present in small quantities in the urine of normal adults.
2. Patients with transitional cell carcinoma of the urothelium have significantly raised levels of urinary CEA in 66 per cent of cases. Diagnostic elevation of plasma CEA occurs infrequently, but when found, is indicative of extravesical disease.
3. We therefore suggest that the measurement of CEA in urine and plasma may be of value in the diagnosis and follow-up of patients with urothelial carcinoma.

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The Evaluation of Transurethral Resection for Benign Enlargement of the Prostate¹

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More than 40 years have passed since the operation of transurethral resection of the prostate was first devised, yet even now its place in the treatment of benign enlargement of the prostate is disputed. In Britain today there are many urologists who limit their use of the resectoscope to annular stenoses of the neck of the bladder, or the palliative relief of an obstructing carcinoma. For a benign adenoma of any size most surgeons still prefer a retropubic or transvesical enucleative operation. There are several reasons for this. On the one hand there is a general belief that transurethral resection is necessarily incomplete in respect of removal of the adenoma, and so has to be done again in many cases; whilst on the other hand there is a widespread opinion that transurethral resection carries a very high risk of perforation, stricture and post-operative incontinence—a risk which, although not unreasonable in the hands of the experts, becomes unacceptably high when surgeons are learning how to do the operation.

In the last decade the senior authors of this paper have gradually come to be performing more and more transurethral resections in gradually larger and larger glands, and their assistants have been learning and doing a substantial proportion of these operations in the course of their training. In view of the criticisms which are so often voiced, we have felt it appropriate to examine our performance and see whether we are justified in continuing to regard transurethral resection as the operation of choice for the benign prostate of all but the largest size.

Composition of the Series (Table I)

1,135 patients with a pre-operative diagnosis of benign enlargement of the prostate were admitted or transferred to our care between October 1964 and December 1971 at The London and St Peter's Hospitals. 935 had a transurethral resection; of these, 198 underwent Millin's retropubic prostatectomy, and 19 had a transvesical procedure. These last 2 are grouped together for the purposes of this survey as "open" operations, and the former are referred to as TURs.

Selection of Cases

In the period covered by this survey it was our policy to offer some type of prostatectomy to virtually every patient who had retention or intolerable symptoms. If a patient was able to sit up in bed without incapacitating breathlessness he was accepted for operation, thanks to the use of epidural or spinal anaesthesia. Hardly any patients were left with an indwelling catheter or a suprapubic cystostomy. In practice only terminally ill patients or those who were completely demented were refused an operation.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

In previous surveys it has been shown that more than 90 per cent of the patients admitted to The London Hospital during the earlier part of this survey with a diagnosis of benign enlargement of the prostate—often a minor part of their overall clinical picture—were operated upon. Cryosurgery and injection of the prostate were not used in the period of this study, though several patients had been subjected to injection therapy prior to transfer.

Table I

Benign Hyperplasia of the Prostate
The London Hospital: 1965-1971

TUR	935
Retropubic	198
Transvesical	21
All open	219
	1,154

Table II

Clinical Assessment of Patients before Prostatectomy

Clinical Grade	TUR		Open		All Cases	
	No.	%	No.	%	No.	%
1	424	45.3	113	51.7	537	46.5
2	393	43.1	88	40.1	481	41.7
3	118	12.6	18	8.2	136	11.8
Total	935	100	219	100	1,154	100

Age

The age range covered by open and transurethral prostatectomy is virtually the same (Fig. 1).

Clinical Condition of the Patient before Operation (Table II).

In view of the wide variety of serious illness which is found among those elderly men who require prostatectomy, it is clearly necessary, in considering results, to separate the relatively young and fit from the obviously aged and decrepit. We have used three clinical grades:

Grade 1. Men under 70 years old: no obvious cardiovascular or respiratory disease. Not diabetic. Regarded as in good general physical condition.

Grade 2. Men between the ages of 71 and 80, and younger men with moderate to severe diabetes, hypertension, chronic bronchitis and emphysema, a previous coronary thrombosis or a stroke more than 6 months before. These were old men, or men who were moderately unfit.

Grade 3. This category was reserved for the very old and the very unfit. Men over the age of 81, and those with a recent cardiac infarct, stroke or pneumonectomy were included in this group. Here also were placed the 9 patients who underwent transurethral resection in spite of their implanted cardiac pacemakers. In many of these patients the prostatectomy was performed in order to rid them of the catheter and allow them to return to a geriatric hospital.

We do not claim that this classification is susceptible of any exact measurement: nevertheless it is offered as some guide as to the kind of patient which we accepted for prostatectomy, and it shows (Table II) that there were more of the very unfit men in the TUR group than in the open-operation group.

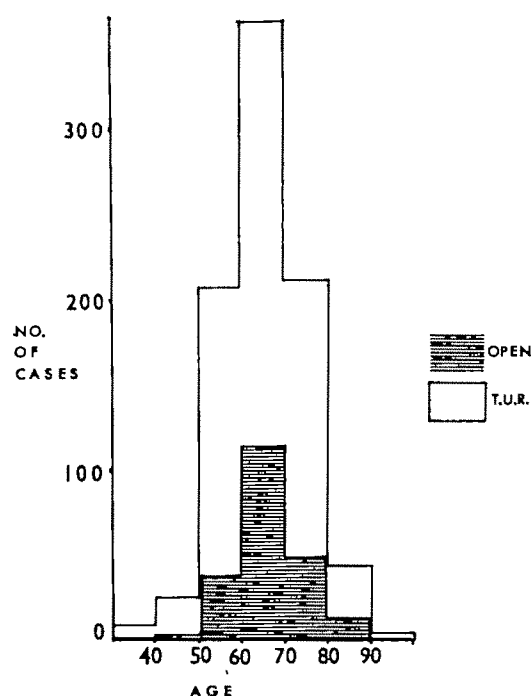


Fig. 1. Age distribution of present series.

Uraemia

Emergency prostatectomy was not performed in this series except on 4 occasions (2 for massive bleeding and 2 because of the unchecked enthusiasm of a newly appointed registrar who subsequently learnt better). The patient who was admitted with chronic retention was as a rule catheterised, had the bladder drained, his blood, fluid and electrolyte deficiencies made good, and then the prostatectomy performed when it was felt that he had been made as fit as possible. In not all these men was it possible, however, to bring the blood urea down to within reasonably normal limits, and in 103 cases the prostatectomy was carried out even though the urea was more than 151 mg per 100 ml. It can be seen that more of these uraemic patients underwent transurethral than open operation (Table III).

Table III
Blood Urea before Prostatectomy

Blood Urea mg/100 ml	TUR			Open		
	No.	Deaths	% Mortality	No.	Deaths	% Mortality
< 50	689	2	0.29	174	3	1.72
50-150	149	7	4.7	36	1	2.9
> 151	97	3	3.1	6	0	0
No data	0	...	...	3	...	...
Total	935	12	1.37	219	4	1.95

Table IV
Weight of Tissue removed at Prostatectomy (GMS)

	TUR		Open	
	No.	%	No.	%
No data	123	13.1	12	5.5
< 5 gm	227	25.1	2	0.9
6-10	297	1.8	0	0
11-20	176	18.8	28	12.8
21-30	61	6.5	32	14.6
31-40	19	2.0	32	14.6
41-50	8	0.8	32	14.6
51-60	12	1.2	19	8.7
61-70	3	0.2	20	9.1
71-80	1	0.1	10	4.6
> 81	8	0.8	32	14.6
Total	935	100	219	100

Table V
Deaths according to Clinical Grades

Grade	TUR			Open			All Cases		
	No.	D.	%	No.	D.	%	No.	D.	%
1	424	0	0	113	0	0	537	0	0
2	393	3	0.76	88	1	1.2	481	4	0.94
3	118	9	7.6	18	3	16.7	136	12	9.2
Total	935	12	1.28	219	4	1.83	1,154	16	1.39

Type of Operation

Transurethral resection was always performed with the avowed object of removing all the adenoma from within the capsule (Blandy, 1971), but certainly in the earlier part of this series, and amongst those cases operated upon by men still in training, the resection was often less than complete. As experience grows, so does the thoroughness with which the adenoma is removed and the capsule exposed. Predictably, there are very many small glands in the TUR series (Table IV, Fig. 2).

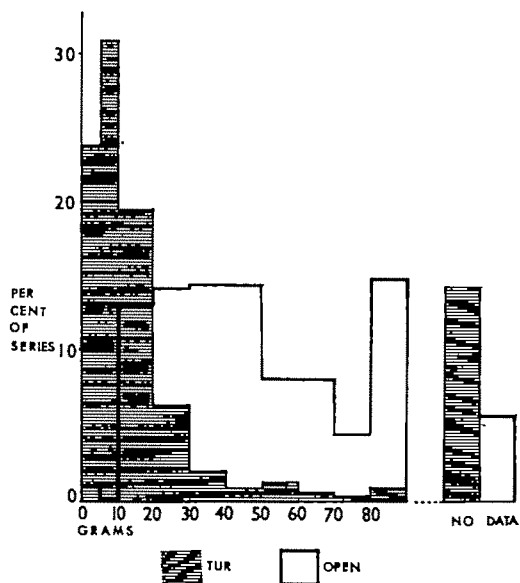


Fig. 2. Distribution of the weight of tissue removed at open and transurethral prostatectomy.

It might be added, of course, that not all the chips from a TUR find their way into the specimen jar, and resection itself tends to make the chips lose weight by desiccation. Nevertheless, what stands out from this table is the comparatively large number of relatively small glands removed, even in this series, by open enucleative operations. More than half these operations were performed for glands weighing under 50 grams.

Results

Operative Mortality (Table V). There were 16 deaths in the 1,154 cases in the first 4 weeks after operation—an operative mortality of 1.39 per cent—a figure which stands comparison with other recently published series. Overall, then we had no reason to fear that our increasing use of transurethral resection was lowering the general standard of work or increasing the danger of operation for our patients.

In 935 TURs there were 12 deaths (1.28 per cent); in 219 open operations there were 4 deaths (1.83 per cent). These figures are no worse than those from other good centres reporting the results of prostatectomy. They do not suggest that limiting open prostatectomy to patients with larger glands has brought about an undue increase in mortality. Open prostatectomy was a little more risky for these patients, but the results are still acceptable by contemporary standards (Ashley *et al.*, 1971).

Predictably, the more ill the group of patients, the higher the mortality.

Table VI
Causes of Death after Prostatectomy

	TUR	Open
Carcinoma of lung	4	0
Pulmonary embolism	1	1
Respiratory and myocardial failure	2	2
Cerebrovascular accident	2	0
Consequences of haemorrhage	3	1
	12 (1.28%)	4 (1.83%)

Haemorrhage. Despite every effort, we have not yet developed an accurate or consistent method of measuring blood loss during and after prostatectomy which may be applied to routine cases, though many such measurements have been made from time to time for the purposes of research. However, as a rough index of blood loss, we have compared the volume of blood given to these

Table VII
Haemorrhage after Prostatectomy

	TUR		Open	
	No.	%	No.	%
Blood replaced at and after operation:				
None	848	90.6	96	43.8
< 2 pints	65	7.0	88	40.2
> 2 pints	18	1.9	35	16.0
Unrecorded	4	0.5	...	...
Post-operative clot retention	15	1.6	2	0.92
Secondary haemorrhage requiring readmission or clot evacuation	9	0.96	1	0.46

patients in the admission in which their prostatectomy by either method took place (Table VII). Clearly there was far less blood replaced after TUR than after open operations. There was very little difference in the proportion of cases needing evacuation for clot retention either in the immediate postoperative period or later on for secondary haemorrhage.

Perforation. Perforation was noticed in 5 transurethral operations in 935 cases (0.5 per cent). No doubt smaller perforations took place more often and went unnoticed. If detected, a transverse abdominal incision was made and the bladder and retropubic space were drained. None of these patients died.

Pulmonary Embolism. A clinical diagnosis of pulmonary embolism was made in 4 out of 935 TURs (0.4 per cent), of whom 1 patient died: it was noted in 5 out of 219 open operations (2.3 per cent), of whom 1 died.

Need for Revision. We expected to find that many more men would need a second or third operation after an initial TUR because of incomplete removal of tissue on the first occasion, and this indeed was found to be the case (Table VIII). In the first 12 months after TUR, more men had to have the operation repeated (2.8 per cent of 935 cases), and in some of these instances the patients had to have residual tissue removed by retropubic prostatectomy. On one occasion, for example, a man had 30 and 24 grams of prostate resected on two successive occasions and still had 65 grams removed at a third and successful retropubic operation. This mortifying experience is not unique

Table VIII

Need for Revision after Prostatectomy

	TUR		Open	
	No.	%	No.	%
Within 1 year of first operation	26	2.8	1	0.5
After 1 year	30	3.2	*	

* None in this series, but 14 of those included in the TUR series had previously had an open operation.

in the annals of transurethral surgery. Nor, unfortunately, is it the case that such misjudgement as to the completeness of the resection is an error confined to the beginner. The two senior authors confess that they still make this mistake, though they make it less often than they did. But having admitted this drawback, it must be pointed out that none of these patients appears to have come to any harm from the need for revision of the resection. Equally, it must be added that if our series had been extended for 2 further earlier years, it would have included 14 patients who had to have a subsequent TUR following a previous retropubic operation.

Stricture. A soft post-meatal stricture is a well-known complication of any kind of prostatectomy, and it is certainly common after transurethral surgery. We were somewhat surprised to see (Table IX) that there was very little difference in the incidence of stricture, either temporary or permanent, in the 2 series of operations.

Incontinence. There were more incontinent patients in the TUR group than in the open prostatectomy group. In part this is explained by the larger numbers in the TUR series, and in part by the inclusion in the TUR series of patients with pre-existing neurogenic lesions of the bladder, especially those who could not urinate after an abdominoperineal excision of the rectum, and men who had recently had a stroke. Even so, the actual incidence of incontinence is no higher in the TUR series than in the open operation cases (Table X).

Infection (Table XI). We were dismayed to learn how many of our patients had developed urinary infection after prostatectomy by either method, when previous research studies from our unit had shown that it was possible to lower the incidence of post-operative infection to about 10 per cent (Webb and Blandy, 1968) in patients in our own wards. Many of the cases operated on in this series were nursed in other wards, by teams less experienced in the aseptic care of the catheter. Such infection cannot be lightly dismissed: if TUR patients became infected, they ran nearly three times the risk of dying after operation than if the urine were kept sterile.

Table IX

Stricture after Prostatectomy

	TUR		Open	
	No.	%	No.	%
<i>Transient</i> (lasting < 6/12)				
Meatus	28	3.0	3	1.4
Elsewhere	7	0.75	4	1.8
All Cases	35	3.75	7	3.2
<i>Permanent</i> (> 6/12)				
Meatus	3	0.3	5	2.3
Elsewhere	2	0.2	2	0.9
All sites	5	0.5	7	3.2

Table X

Incontinence after Prostatectomy

	935 TURs		219 Open ops.	
	No.	%	No.	%
Neurogenic bladder	4	...	...	...
After abdominoperineal resection	2	...	...	...
Tuberculous contracted bladder	1	...	...	...
Attributable to operation	2	(0.2)	4	...
Total	9	0.96	4	1.8

Table XI

Infection after Prostatectomy

	TUR		Open	
	No.	%	No.	%
<i>Men with sterile urine before operation</i>	829		171	
Infected afterwards	147	17.7	35	19.0
Epididymitis	0	...	0	...
Died	9	1.1	3	1.6
<i>Infected urine before operation</i>	106		34	
Epididymitis	2	0.2	2	1.2
Died	3	2.8	1	2.9

Epididymitis. In the earlier part of this series it was our practice to ligate the vasa deferentia at the time of open operation. We did not do this at transurethral resection. Gradually we began to give it up even in open cases until in the past 4 years it has been performed very seldom indeed. The low incidence of epididymitis found in this survey does not suggest that there is any need to revert to the former practice (Table XI).

Antibiotics. Throughout the entire series, prophylactic antibiotics were never administered. Antibiotics were given to men whose urine was infected prior to prostatectomy, or when infection occurred afterwards, or if their bronchitis demanded them.

Hospital Stay. Unfortunately this study was not designed to note the bed-days occupied by these patients. Our own experience, however, is supported by a recent survey of the mean stay in hospital of 20 consecutive TUR patients compared with 20 consecutive open prostatectomies: the mean hospital stay for TUR cases was 8 days, for open cases 18 days. A further and more comprehensive study of this aspect is now in hand.

The Patient's Appraisal of his Operation. We noted the comments which had been recorded in the notes at the out-patient follow-up visits. Unfortunately not all the patient's comments were in

Table XII

Patient's Appraisal of Prostatectomy

	TUR		Open	
No data available	131		25	
Data available	804		194	
	No.	%	No.	%
Very good	551	68.5	150	77.4
Improved	232	28.8	41	21.1
No change	13	1.6	1	0.5
Worse	9	1.1	2	1.0
Total	804	100	194	100

the notes, and quite possibly some dissatisfied patients had taken themselves off to other hospitals, though, if so, we had not been requested to furnish other surgeons with details. In the event we have an incomplete sample of 998 patients (804 TURs and 194 open cases). As Table XII shows, there is little difference, as far as the patient can tell, in the end-result of a TUR or an open prostatectomy.

Discussion

This survey, however retrospective and however incomplete, shows that the increasing use of transurethral surgery has not led to an increased mortality or morbidity following prostatectomy. On the contrary, a TUR requires less blood, is perhaps slightly safer than an open operation, and needs a considerably shorter hospital stay for the patient.

The operations in this series were not only performed by consultants but also by men in various stages of their urological training. The study suggests that responsible urological trainees, under appropriate supervision, do not necessarily cause an unacceptable amount of incontinence or an undue number of perforations. Transurethral resection has a valuable part to play in the manage-

ment of the benign prostate: it is difficult to do well, and unless done well, is dangerous; but it can be taught, and learned, and practised. The authors believe that this is one of the most valuable contributions which the urologist can offer, and one of the most important reasons why specialist urologists and urological units are needed today.

Summary

The results of 870 TURs are compared with 205 open prostatectomies performed over a period of 6 years.

The age range of the two series was similar, but the TUR cases were less healthy, and the open operations were on the whole performed for larger glands.

Overall mortality for the series was 1.49 per cent: for TUR 1.38 per cent: for open operations 1.95 per cent.

Stricture, incontinence and post-operative infection were similar. 2.9 per cent of the TUR patients required a revision operation within the first year, presumably for incomplete removal of adenoma at the first operation.

Patients were no less pleased with the results of TUR than open prostatectomy.

The duration of hospital admission for TUR is less than half that needed for an open prostatectomy.

We wish to thank Miss Eileen Walden of The London Hospital and Miss Rachel Gregory of St Peter's Hospitals for making hospital notes available, and Mr R. Singh for help in extracting information from the notes.

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Long-term Follow-up Results with the Pubo-vaginal Spring Device in Incontinence of Urine in Women; Comparison with Electronic Methods of Control¹

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The pubo-vaginal spring device for the control of incontinence of urine in women has been described on two occasions (Edwards, 1970, 1971). The device was first designed in 1965, and has been in clinical use for 4 years, and available in its present form for 3 years.

PROFILE

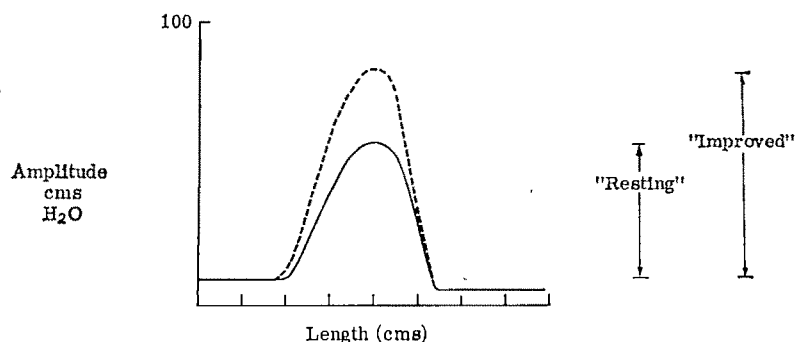


Fig. 1. Urethral pressure profile recording showing an increase in the profile amplitude when a device for controlling incontinence is *in situ*.

The early reports suggested that the device could be a useful way of treating incontinence of urine in women, in particular resistant incontinence, that is incontinence that has failed to respond to one or more attempts at control by conventional surgical methods.

This paper presents the details of the results obtained in a further group of patients in which control of incontinence was attempted with the device. The objects of the study were to assess the long-term results obtained with the device, to correlate the results with the objective methods of selection employed, and to compare the success rates of the device with those obtained in a larger, but comparable group of patients treated with electronic devices.

The series consists of 2 groups, the first of which was made up of 42 patients treated with the spring device. Of these 42, only 4 had been carried over from the previous series. The second group was made up of 65 patients treated electronically.

¹Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

Method of Selection

The use of a particular device depended on the results of two objective tests.

The first of these was the urethral pressure profile (Brown and Wickham, 1969). The patients were first studied under control conditions, and a "resting" profile obtained. Further recordings were carried out with an electronic or mechanical device *in situ*, the "improved" profile recordings superimposed on the control profile as described by Harrison and Constable (1970) (Fig. 1). The device chosen for clinical use was that which produced the greatest improvement in the profile amplitude. If the first device chosen failed to produce any benefit, then the device producing the next best improvement in the profile amplitude was prescribed.

The next objective test carried out was filling cystometry. Devices were used in the presence of cystometric abnormalities early in the series, but the reports of Harrison (1970, 1971) suggested that the success rates should be higher if the use of the devices was confined to patients whose cystometric curves were normal and whose sole defect was presumed to be sphincter weakness. This second criterion was subsequently applied.

Results

Of the 42 patients studied, 36 had sphincter weakness and 6 detrusor dysfunction. The success rates are shown in Table I. The overall success rate in the 42 cases treated with the spring device was

Table I
Overall Success Rates

Type of Incontinence	Spring		%	Electronic	
	No. of Patients	Success		% success	No.
Sphincter weakness	36	25	69.5	37	54
Detrusor dysfunction	6	4	66	31	13
Combined problems	...	...	...	75	4
Total	42	29	69	41.5	71

69 per cent, compared with 41.5 per cent in those treated by electronic methods. The number shown in the extreme right-hand column at the bottom (71), referring to electronic methods of control, exceeds the total number of patients in which this method of control was attempted because several patients were treated with more than one type of electronic device.

The follow-up results of the 29 patients treated successfully with the spring device are shown in Figure 2. The longest period of follow-up was just over 4 years, and the shortest 5 months. Ten patients treated successfully with the spring device had been treated unsuccessfully by electronic methods. Ten patients continue to use the spring device as a sole method of urinary control.

Nine patients used the device while awaiting surgical repair, the interval varying from 6 months to 18 months, and 3 patients continue to use their devices on this temporary basis.

Five patients stopped using their devices. One, an enuretic patient, reported herself cured; 3 found themselves incapable of removing and inserting the device after satisfactory use for some months, 2 because of worsening arthritis, and 1 following a severe hypertensive episode. Two patients discontinued the use of the device for aesthetic reasons, despite satisfactory control, and 1 of these had abandoned an electric pessary for the same reason. One patient was lost to follow-up after 9 months; when last seen she reported success with the device.

FOLLOW-UP

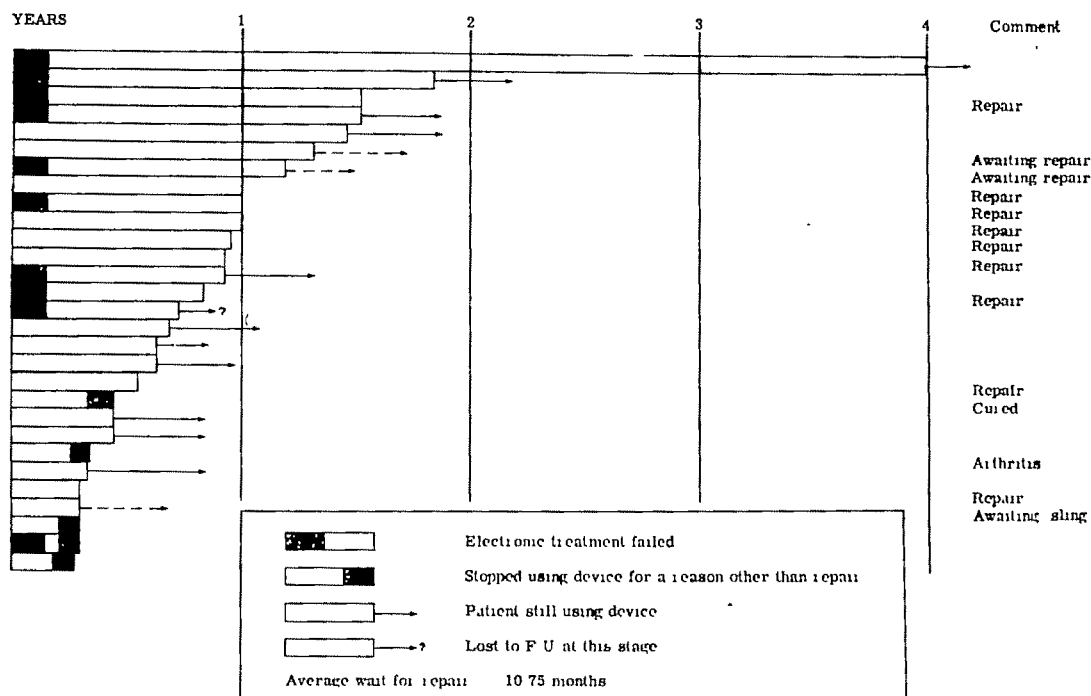


Fig. 2. Long-term follow-up results with the pubo-vaginal spring device.

Table II
Success Rates related to Age

Age (years)	Spring		%	Electronic	
	No. of Patients	Success		% success	No.
0-20	0	..	...	75	8
21-30	2	1	50	60	5
31-40	2	1	50	75	6
41-50	14	10	71	33	18
51-60	13	8	61	43	14
61-70	8	7	87.5	0	5
70+	3	2	66	22	9
Total	42	29	69	41.5	65

Comparative Results. Table II shows the success rates obtained with the 2 types of devices in relation to age. As far as treatment with electronic devices was concerned, it appeared that the older the patient, the less likely was a successful outcome. The highest success rate with the spring device was seen in the 61 to 70 age-group, in which 7 patients out of 8 reported success. Age does not therefore appear to affect the success rate in the case of the spring device.

Table III correlates the success rates to the combined factors of previous surgical repairs and the patients' parity. The figures relating to electronic treatment differ slightly from those reported in our other communication (Edwards and Malvern, 1972), but the trend was the same in that the success rate fell markedly in relation to increasing parity and previous unsuccessful surgical

Table III

Success Rates related to Repairs and Parity

Group	Spring		%	Electronic	
	No. of Patients	Success		% success	No
No children No repairs	6	4	66	63	19
Repairs No children	5	4	80	50	10
Children No repairs	12	8	66	40	10
Children Repairs	19	13	68.5	23	26
Total	42	29	69	41.5	65

Table IV

Profile Analysis 1—to assess the comparable nature of the two groups, the group treated with the spring device, and the group treated electronically

	Spring	Electronic	P
<i>Success</i>			
Mean age (years)	54.689	37.444	< 0.0005
Mean profile amplitude—"resting" (cm H ₂ O)	31.115	33.222	...
Mean profile amplitude—"improved" (cm H ₂ O)	56.000	54.346	...
<i>Failure</i>			
Mean age	50.538	48.81	...
Mean profile amplitude—"resting" (cm H ₂ O)	29.916	36.428	...
Mean profile amplitude—"improved" (cm H ₂ O)	57.888	48.205	...

procedures. This trend did not appear to be present in the case of the spring device, and a success rate of 68.5 per cent was seen in a group of 19 patients who had borne children and who had been subjected to previous repairs, compared with a 23 per cent success rate in a group of 26 similar patients treated electronically.

In order to establish the comparable nature of the 2 groups treated with the different devices, successes and failures in each group were analysed with regard to age, the "resting" profile amplitude, and the "improved" profile amplitude. The only significant difference seen (Table IV) was that the mean age of the patients treated successfully with the spring device was higher than that of the patients treated successfully with electronic devices ($P < 0.0005$). The groups appeared to be identical in all other respects.

As with electronic methods of control, the basic working hypothesis with regard to selection of patients for treatment was that an increase in the profile amplitude would indicate that a successful outcome would result from the use of the device producing that profile increase. However, analysis of the results (Table V) showed that all cases demonstrated a statistically significant increase in the profile amplitude, although the increases in the cases showing a successful outcome were more significant. The urethral pressure profile would not seem to be of value in selecting cases for treatment with a spring device, confirming our report of its inaccuracy as a prognostic test for the prescription of an electronic device. Random allocation of the spring device may therefore

Table V

Profile Analysis 2—relation of increases in the profile amplitude to success rates

	"Resting" Profile Amplitude (mean values—cm H ₂ O)	"Improved" Profile Amplitude (mean values—cm H ₂ O)	"Improved" "Resting"	P
<i>Spring Device</i>				
Success	31.115	56.000	1.805	< 0.0005
Failure	29.916	57.888	1.785	< 0.01
<i>Electronic Devices</i>				
Success	33.222	54.346	1.638	< 0.0005
Failure	36.428	48.205	1.325	≈ 0.01

be suggested, and no reduction in the success rate should ensue. If treatment by electronic methods is preferred, then it could be suggested that a profile amplitude increase by a factor of at least 1.6 is necessary for success to be likely, but from our experience we would not attach much importance to this arbitrary figure.

Conclusion

In 4 years of clinical experience with the pubo-vaginal spring device only one complication has been reported, and this case was described in the last series.

No intravaginal device is entirely comfortable when in use, and added to this drawback, the spring device needs to be removed each time the patients need to pass water, and subsequently re-inserted. The spring device is, however, lighter in weight, cheaper, less cumbersome, and often simpler to use and more reliable than the commercially available electronic devices. From this comparative series it would also appear to be more likely to be beneficial to the patients, especially those patients in whom other methods of treatment have failed.

The results reported in this series confirm those previously described, and we would suggest that the device has a definite role to play in the management of resistant incontinence, in the control of incontinence in patients who do not wish to have an operation or who are unfit for surgery, and in the temporary control of incontinence in patients who are on long waiting lists for repair procedures to be carried out.

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One of us (L. E.) carried out this work as part of the requirement of the M.Chir. Degree of the University of Cambridge.

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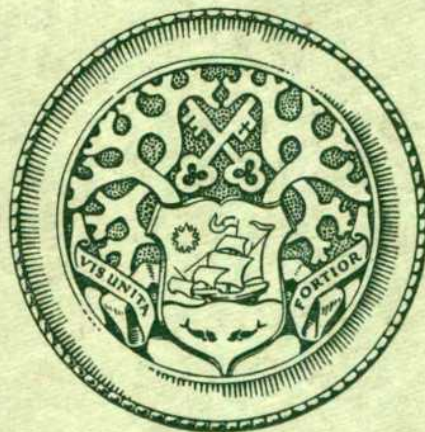
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April 1973

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(1) *Postgrad med J.* (1971), (September Supplement), 47, 7.

(2) *Brit med J.* (1969) *i*, 541.

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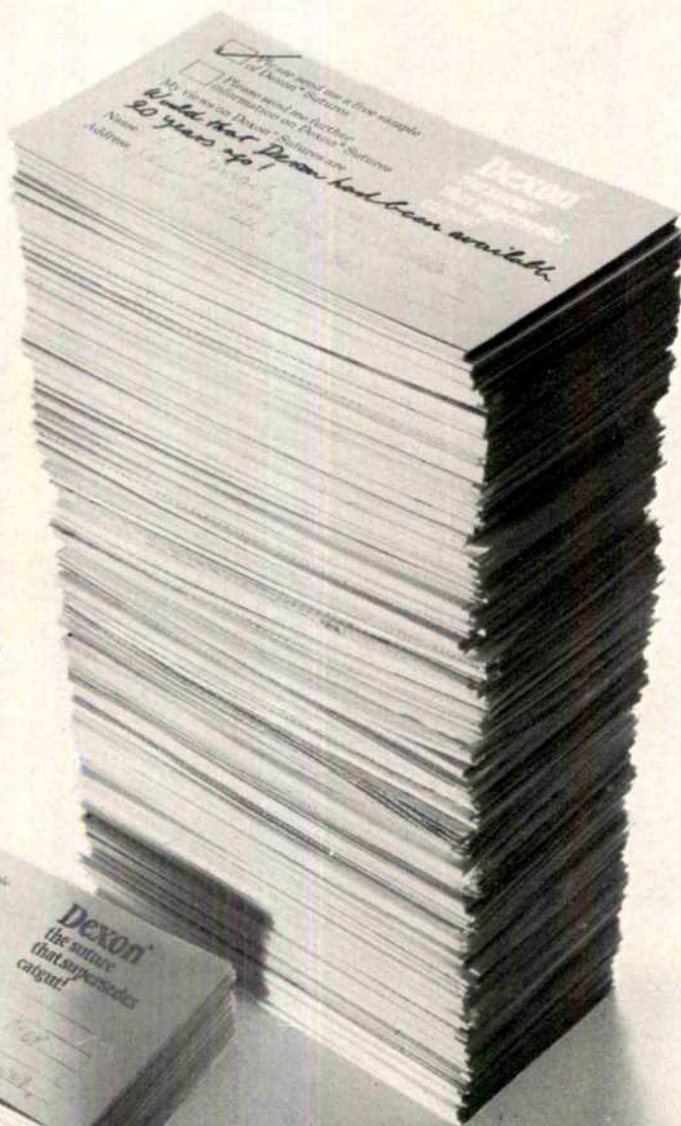
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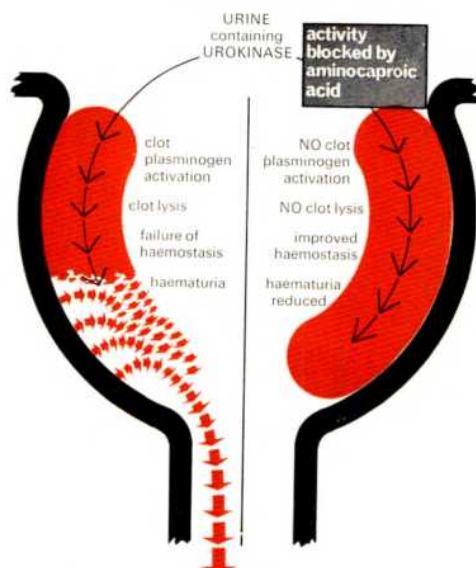
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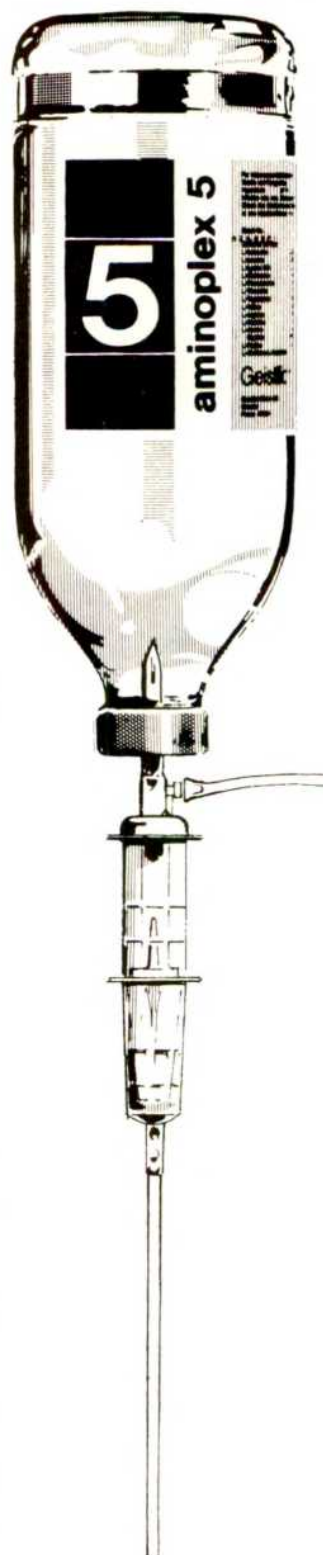
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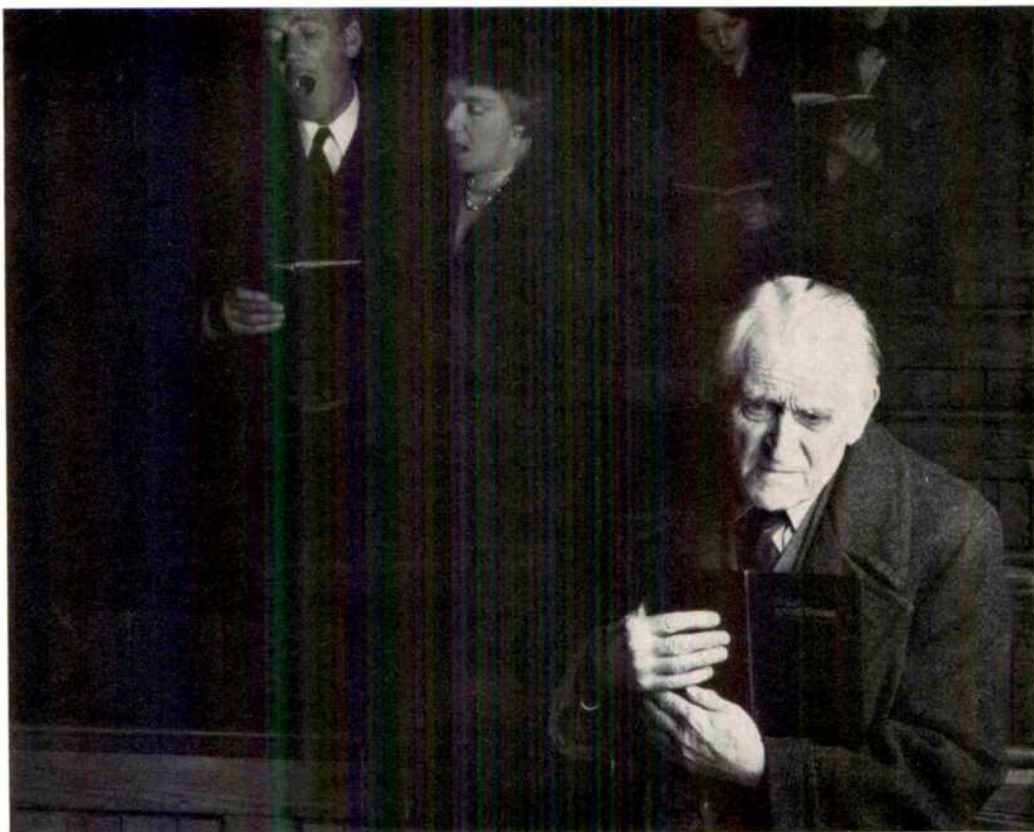
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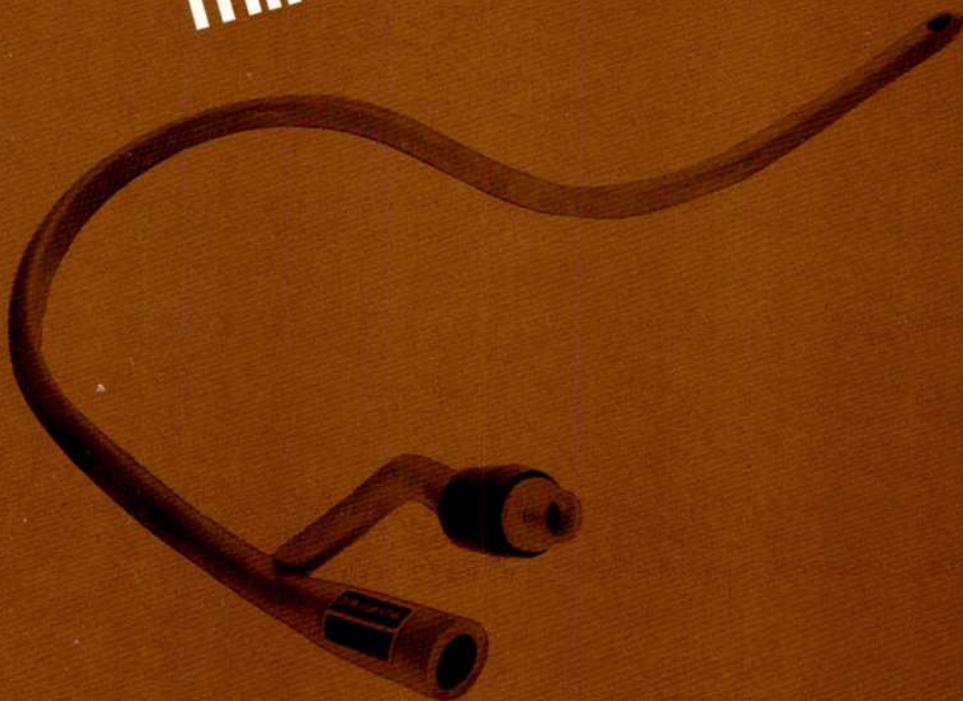
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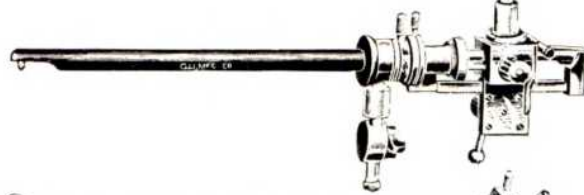
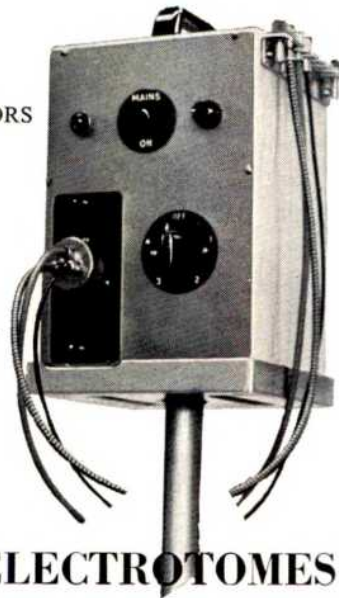
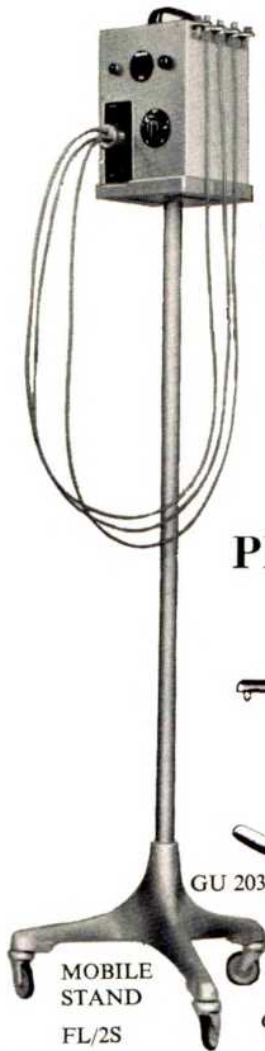
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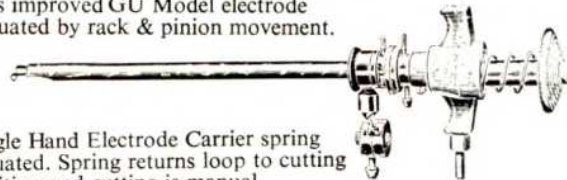
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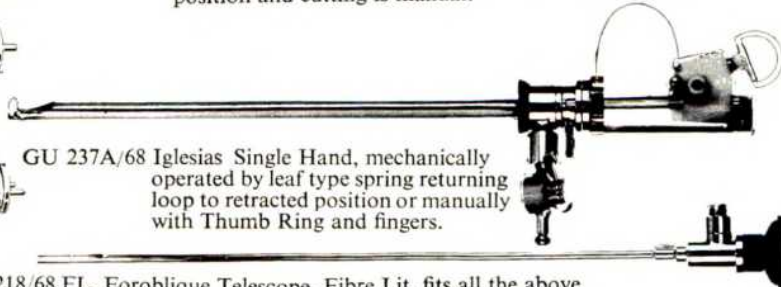


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1. Brit. Med. J., 1972, 3, 13.
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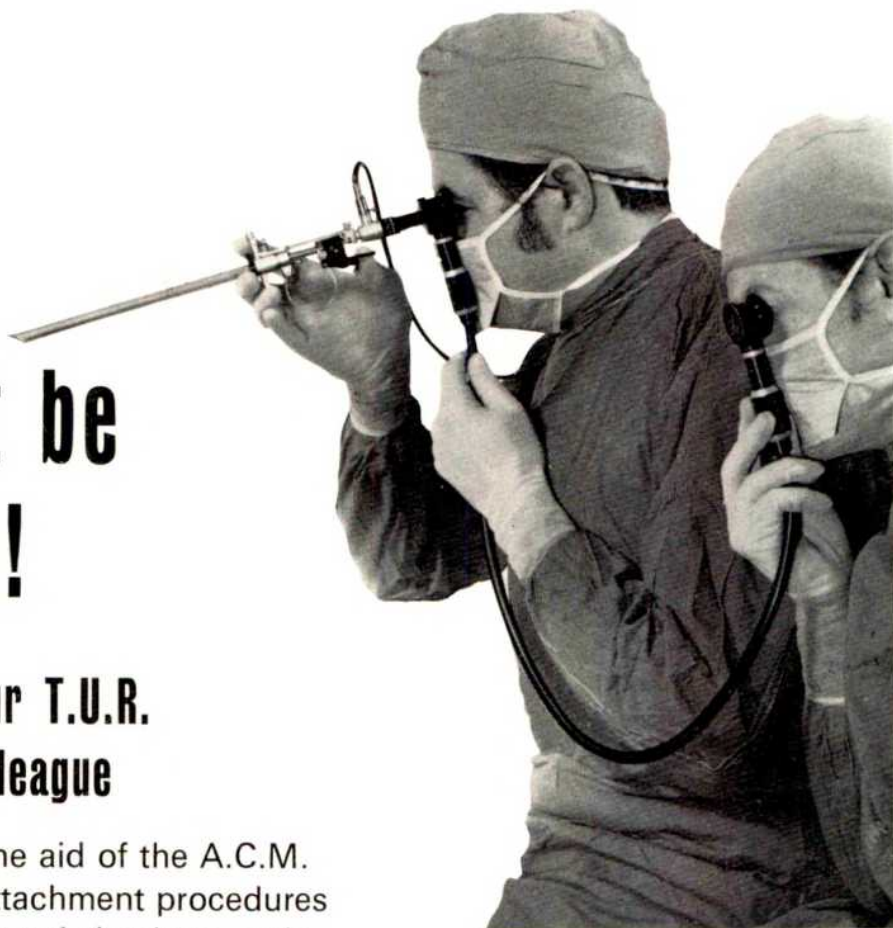
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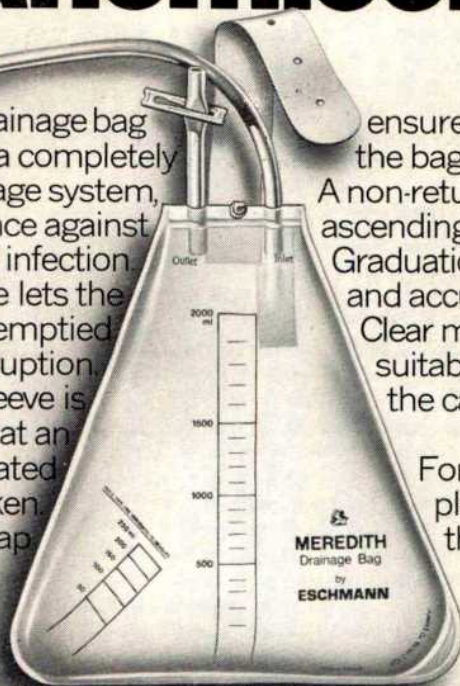
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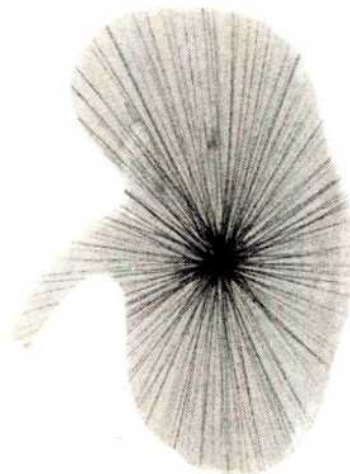
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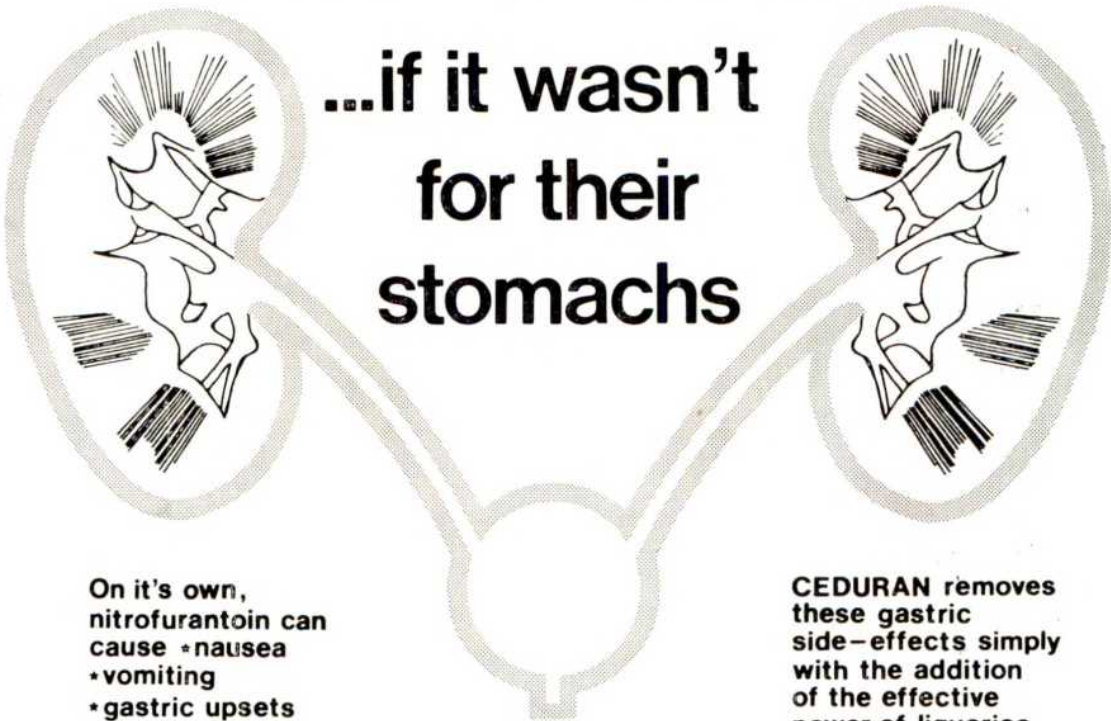
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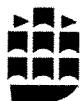
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Division of the External Sphincter¹

N. O. K. GIBBON

Liverpool Regional Urological Centre, Sefton General Hospital, Smithdown Road, Liverpool

Historical Review

Division of the external sphincter is now firmly established as a safe and effective procedure for the relief of urethral obstruction in selected cases of paraplegia in the male. The technique is fairly well standardised but some confusion still persists regarding the indications for the operation, and the object of this paper is to assess the place of external sphincterotomy in relation to the overall urological management of the paraplegic. For this purpose the historical approach has obvious advantages. A convenient starting-point is the belief which was almost universal 50 years ago and which persists in some quarters to the present day that to operate for retention in the neurogenic bladder is to court the risk of complete incontinence. Emmett exploded this myth in 1937 when he showed that a small bladder neck resection improved the control of a patient with spastic paraparesis whose large residual urine had been aggravating his frequency, urgency and incontinence (Emmett and Green, 1963). The operation had been prompted by the observation that in similar cases measurement of the residual urine by catheterisation had been followed by a much longer spell than usual before the next voiding. Emmett attributed the obstruction to involvement of the bladder neck, as the lower edge of the detrusor, in the hypertrophy and spasticity affecting that muscle over the years. Such changes are now recognised as being secondary to external sphincter obstruction and associated with good bladder neck opening (Ascoli, 1967; Currie *et al.*, 1970). Probably chronic inflammatory changes provided the main obstructive element and these are much less common nowadays.

Bladder neck resection subsequently found its physiological application in cases with lesions of the sacral segments in which there are no detrusor contractions to pull open the bladder neck. Emmett went on to demonstrate radiologically obstruction at the external sphincter level in spastic cases with retention persisting after adequate bladder neck resection (Emmett *et al.*, 1948). By an anaesthetic block of the sacral roots or internal pudendal nerves he was able to relax the urethra and he suggested that subarachnoid alcohol block, pudendal neurectomy or sacral rhizotomy might be effective permanently. In one case operated upon, pudendal neurectomy failed, perhaps for technical reasons, but lumbo-sacral rhizotomy was later effective. Satisfaction with the results of these procedures, which were widely adopted, was soon tempered by their unreliability and by the high incidence of sexual impotence which followed them (Gibbon, 1966). A direct attack on the spastic external sphincter soon began to seem attractive.

At this stage it is necessary to go back some years to follow another line of thought. Obstruction at the external sphincter level *in the absence of spasticity* had already been demonstrated by Watkins (1936) in a series of cauda equina cases. He attributed the condition to pressure and elasticity of the tissues surrounding the triangular ligament, the nature of which will be considered later.

Both types of obstruction have been featured in reports of direct surgical intervention at the level of the membranous urethra, though sometimes insufficient data are available to enable the case to be classified one way or the other.

¹Read at the Twenty-eighth Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

Donovan (1947) wrote: "With a cauda equina bladder the proper course may be to remove permanently the obstruction to urination in the region of the triangular ligament and to allow the penis to drain into a urinal". He suggested that a rectus fascial sling or gracilis transplant might be used later to restore continence, but after his single reported operation (done with the

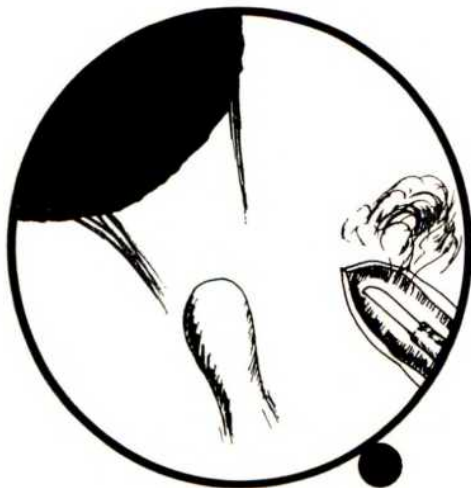


Fig. 1

Fig. 1. Commencement of diathermy incision at the level of the verumontanum. The mucosal cut edges have retracted and the transverse muscular fibres are being divided a few at a time using the minimum coagulation current required.



Fig. 2

Fig. 2. The completed upper end of the incision is shown. Low down is an arterial spurt and higher up venous bleeding where the muscle wall has been breached accidentally.

cold punch) the obstruction recurred in 3 months. A year later Baumrucker (1948) reported 3 cases of spastic external sphincter obstruction treated by coagulation with the diathermy loop. In 2 the obstruction was relieved, and in 1 the residual urine was reduced. Semans (1949) conceived the idea of a peripheral denervation to be achieved, through a perineal approach, by freeing the

membranous urethra from the peri-urethral tissues just below the prostate using a goose-necked clamp ("membranous urethrolisis"). Only a single case was reported. In the same paper, the author described a "membranous urethroplasty" which he had carried out in 16 cases of paraplegia complicated by obstruction at the level of the external sphincter. The operation consisted of transection of the urethra just below the apex of the prostate, which was then sutured down to the urogenital diaphragm around a catheter. The result was a shortening of the urethra with a 20 per cent reduction in the resistance at that level which is implied to have been non-spastic. This seems unlikely in at least some of the cases from a consideration of the neurological levels and the high urethral resistances recorded. One patient developed a stricture, but in 12 of the cases followed for 7 to 15 years (Semans and Bunts, 1961) satisfactory results were observed.

There can be no doubt that direct operations on the external sphincter were occasionally being carried out by other workers about this time. For example, Baker *et al.* (1950) included the proximal edge of the external sphincter during a bladder neck resection in 1 case while Burns and Kittredge (1958) considered it justifiable to resect the same tissue if bladder neck resection failed. Bors and Comarr (personal communication) had also divided the external sphincter in 1 case prior to 1957.

The first 10 cases of external sphincterotomy reported from the Liverpool Regional Paraplegic Centre (Ross *et al.*, 1957) were done for non-spastic obstruction. All had been subjected to subarachnoid alcohol block or pudendal neurectomy and 4 of them had had a bladder neck resection. The cold punch was used and haemorrhage was troublesome. One patient who had gross urinary infection pre-operatively succumbed to repeated secondary haemorrhage while one other who died from uraemia was known to have bilateral ureteral reflux with hydronephrosis and poor renal function. Five of the surviving 8 had their residual urine reduced to nil by the operation and the others to a few ounces. Of our next series of 30 patients (Ross *et al.*, 1963) only 2 had undergone subarachnoid alcohol block or pudendal neurectomy, reflecting our anxiety to avoid inflicting impotence, but most had had a bladder neck resection. In many cases the obstruction was spastic. Using a Colling's diathermy knife through a panendoscope, incisions were made posterolaterally from the level of the verumontanum downwards for approximately 3 cm dividing the muscular wall of the urethra subtotally (Fig. 1). Bleeding arteries were controlled with the ball electrode, and venous bleeding which was not responsive to this approach fortunately subsided rapidly on insertion of a catheter (Fig. 2). In all but 2 cases the residual urine was abolished or considerably diminished. In a 10-year review of the results of the operation (Ross *et al.*, 1967) 25 further cases were included. An interesting tendency observed was for external sphincterotomy to be carried out increasingly as a primary procedure in supra-sacral lesions. The effect of the operation was shown to have been well maintained over the years and only 5 of the 65 patients had required a permanent catheter, all except 1 of these being paraplegic of non-traumatic origin. Up to the end of 1971 division of the external sphincter had been carried out at our Centre 176 times in 155 patients with no mortality after the 2 early cases already mentioned. The effectiveness and safety of the operation have been amply confirmed from other Paraplegic Centres with a combined experience approaching 300 cases (Smythe, 1966; Currie *et al.*, 1970; Key, 1970; Bors and Comarr, 1971; Elsaesser and Stoephaseus, 1972; O'Flynn, 1972). From these reports it appears that the operation has been done for both spastic and non-spastic obstruction and with increasing frequency as a first procedure in supra-sacral lesions.

Rationale of External Sphincterotomy

The tubular extension of the external sphincter up towards the bladder neck is now well recognised, but the function of the muscle as a whole is still subject to controversy. It appears that, in the supine position at least, the sphincter contributes little to the retrograde posterior urethral resistance which is on average about 75 cm of water (Lapides *et al.*, 1960). This is largely due to smooth muscle innervated by the sympathetic (Donker *et al.*, 1972). The striated sphincter prob-

ably provides the increased resistance found in the standing position (about 120 cm of water—Lapides *et al.*, 1960) as well as that required to resist sudden increases of intra-abdominal pressure and to interrupt quickly the urinary flow.

In spastic paraplegia the retrograde urethral resistance is usually greater than 50 cm of water (Bors and Comarr, 1971) and averages 70 cm of water (Currie *et al.*, 1970), which is approximately normal. The retention in these cases is normally due to dyssynergia between the detrusor and the external sphincter as well as to contractions of the external sphincter during flexor spasms when pressures of well over 100 cm of water are reached. In sacral lesions the resistance is variously reported to be less than 50 cm of water (Bors and Comarr, 1971) or to average 50 cm of water (Currie *et al.*, 1970). These pressures are considerably lower than those usually generated by abdominal straining or manual compression but it must be remembered that the sphincter resistance is usually measured in the supine position. Vincent (1966) has suggested that when these patients are in the sitting position there is a "bunching up" of the membranous urethra against the perineal membrane due to the bladder and prostate sagging downwards between the flaccid levatores ani. Vincent also considered the possibility of angulation of the membranous urethra due to falling backwards of the bladder and prostate, and Dollfus (1972) has confirmed this mechanism radiologically in one case in which the obstruction was relieved by prostato-cystopexy. To test the effect of posture we have recently determined the retrograde urethral resistance in 13 of our own cases in the supine and sitting positions and with the bladder full or empty, using the simple technique described by Ross and Tinckler (1959). Invariably the figures were higher (up to +37 cm of water) in the upright position whatever the degree of sacral reflex activity. In the supra-sacral lesions the normal pelvic floor reflexes may have been responsible. As far as sacral cases are concerned Vincent's hypothesis is attractive, but in view of the findings of Donker *et al.* (1972) further research is indicated to elucidate the part played by sympathetic smooth muscle innervation. Contrary to expectations the resistance with a full bladder was almost always rather less than with an empty one, in either position. Evidently the overall weight of the abdominal viscera is the overriding factor while perhaps the full bladder gets more support from the levatores ani than an empty one. The difficulties besetting analysis of the obstructive factors in the neurogenic bladder are partly due to the fact that, in supra-sacral lesions (*i.e.* those cases with positive bulbo-cavernous and anal reflexes), the degree of reflex activity shown by the bladder, the external sphincter and the pelvic floor muscles generally is very variable from patient to patient and from time to time. In every case, therefore, these factors must be re-assessed carefully at each stage when surgery is being contemplated.

After division of the external sphincter for dyssynergia and spasticity the patient usually voids by reflex detrusor contraction with a low residual urine. He is still subject to uninhibited micturition but usually with less frequency. Stress leakage is not a serious problem. When the operation has been done in sacral lesions for non-spastic obstruction the patient will usually have had a bladder neck resection previously. Voiding will occur by abdominal straining or manual compression and will be required at less frequent intervals. Stress incontinence is usually less troublesome than before the operation, due to avoidance of the high intravesical pressures accompanying over-distension. Radiologically, the narrow zone in the membranous urethra can be shown to have opened up while measurement of the retrograde urethral resistance shows a variable reduction. In the series reported by Currie *et al.* (1970) the average decrease in patients with reflex neurogenic bladders was 25 cm of water (10 to 49 cm of water). In patients with sacral lesions the average fall in pressure was 14 cm of water. No greater drop in pressure was found in cases in which an anterior incision had been made in addition to the bilateral ones. Our own findings have been similar, and an interesting feature has been the abolition in some cases of the pressure variations observed pre-operatively with changes of posture. Smythe (1966) has recorded the urethral pressure profile in a paraplegic with reflex bladder contractions before and after division of the external sphincter. An almost complete absence of the high-pressure zone was observed and the intravesical and urethral pressures were almost equal.

The Place of Division of the External Sphincter

Sacral Lesions. In many cases abdominal straining is sufficient to force open the bladder neck which lacks the support of the levatores ani and tends to funnel more readily than usual. If there is troublesome residual urine, micturating cysto-urethrography will show the level of the obstruction and indicate the need for a bladder neck resection or external sphincterotomy. Sometimes the bladder neck resection (or prostatectomy) shows up the need for relaxation lower down and has to be followed by an external sphincter division.

Supra-sacral Lesions. In the presence of good detrusor contractions there is no indication for bladder neck resection in this type of case. (Prostatic obstruction and inflammatory stenosis must be excluded.) Failure to empty the bladder will usually be an indication for division of the external sphincter. A special problem arises in the patient with positive bulbo-cavernosus and anal reflexes whose rehabilitation is progressing well and yet who has no evidence of return of reflex detrusor activity. The only alternative to a more or less prolonged period with an indwelling catheter seems to be a bladder neck resection followed, if necessary, by external sphincterotomy in the hope that extrinsic pressure on the bladder wall will achieve efficient emptying. With the increasing pressure on paraplegic beds nowadays we have had to resort to early operation in this type of problem and we have had no cause to regret the intervention.

Summary

Division of the external sphincter may be required for obstruction at that level with or without evidence of spasticity.

In supra-sacral lesions with good detrusor contractions there is normally no indication for a bladder neck resection and, when necessary, external sphincterotomy can confidently be carried out as a primary procedure.

In sacral lesions, bladder neck resection may be required as a substitute for the normal opening mechanism, and this may have to be followed by division of an obstructive but non-spastic external sphincter region.

The operation shows up favourably as regards simplicity, safety, effectiveness and freedom from complications when compared with the alternative procedures which have been suggested.

The author is indebted to Dr I. Nuseibeh for his painstaking manometric work.

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The Damaged Human Detrusor: Functional and Electron Microscopic Changes in Disease¹

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Vesical overdistension gives rise to both functional and ultrastructural changes (Lloyd-Davies *et al.*, 1970; Lloyd-Davies and Hinman, 1970; Lloyd-Davies and Hinman, 1971; Mayo, 1971). Following animal experiments, pressure, flow and ultrastructural bladder changes have been studied in patients following vesical overdistension, and in a variety of other conditions. The results form the basis for this paper.

Materials and Methods

Intravesical and rectal pressures were recorded by the method described by Claridge and Shuttleworth (1964). The voiding flow rate was simultaneously recorded by an induction flow meter, urine being collected by funnel with the patient seated (Fergus, 1969).

Bladder biopsies were taken and examined in 30 patients. The biopsies were taken with Lowsley's forceps from the posterior wall of the bladder. A deep biopsy including an adequate amount of muscle was necessary and no complications occurred.

The piece of muscle obtained was fixed in 4 per cent methanol-free formaldehyde in cacodylate buffer pH 7.4 for 4 hours before being cut into 1 mm³ blocks, post-fixed in Palades sucrose fixative for 1 hour and embedded in Epon. 1 mm sections stained with 1 per cent toluidene blue were examined by light microscopy for inflammatory cells. Ultrathin sections, stained with lead citrate and uranyl acetate were examined in an Elmiskop I electron microscope.

Results

Four patients are reported here, illustrating the functional changes which may occur following a single episode of overdistension.

Case 1. V. McG. Female, age 29. This patient had a 48-hour episode of retention following childbirth and was found to have a residual urine volume of 2,500 ml. The bladder was atonic for 3 weeks, but voiding was re-established with carbachol. The micturating cystometrogram showed a normal voiding pattern 2 months after the overdistension episode (Fig. 1).

Case 2. A. P. Female, age 24. This patient also had a 24-26 hour period of retention following delivery of twins, with development of a paravaginal haematoma. She voided by manual expression, and after 18 months a partial cystectomy was carried out to reduce bladder size because of poor emptying and recurrent infection. The result of the operation was reasonably satisfactory for 6 months, but the patient then became incontinent of urine. The micturating cystometrogram showed the incontinence to be due to the straining pattern of micturition (Fig. 2). A subsequent Marshall-Marchetti operation and finally a caecocystoplasty failed, and the patient ultimately underwent urinary diversion by an ileal conduit.

¹Read at the Twenty-eighth Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

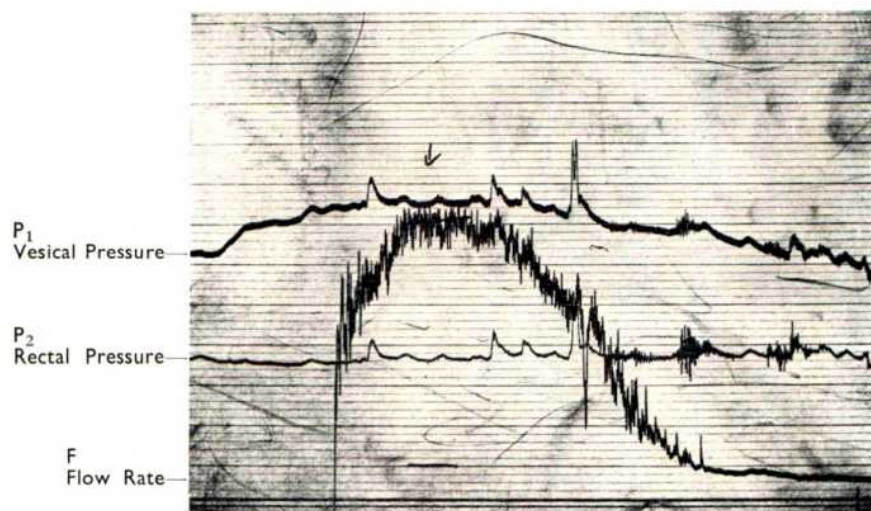


Fig. 1. Case 1. Normal micturating cystometrogram (M.C.M.).

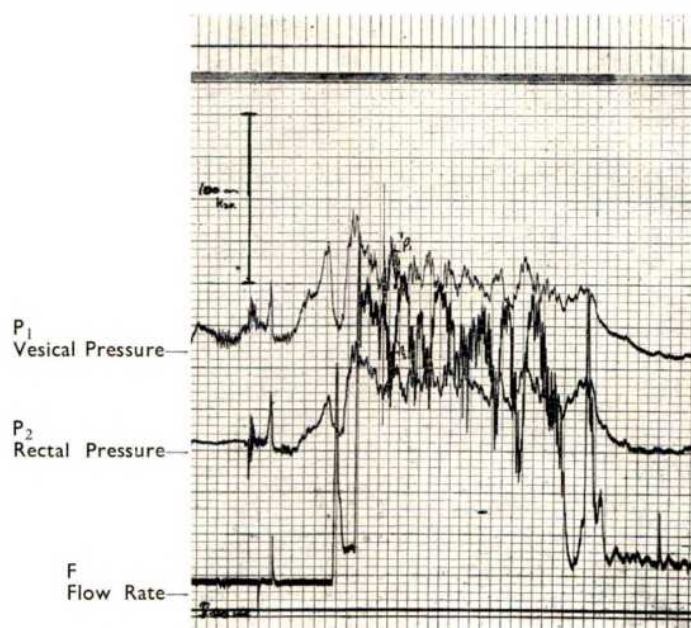


Fig. 2. Case 2. M.C.M. shows voiding by raising abdominal pressure.

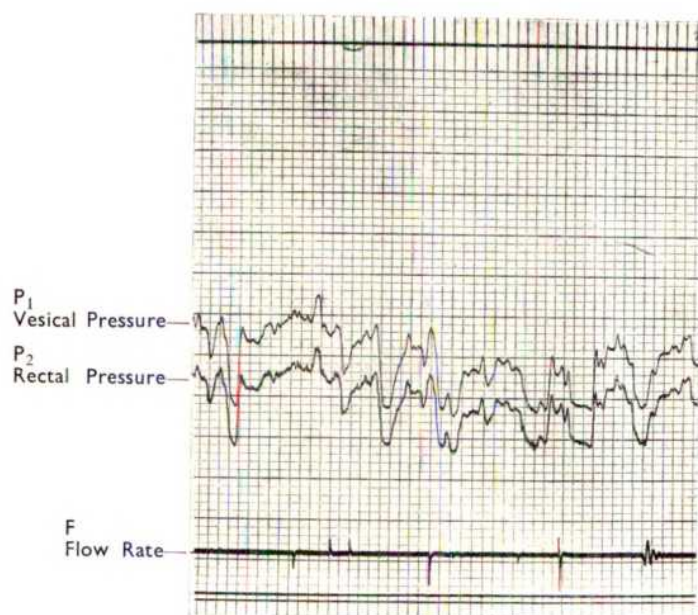


Fig. 3. Case 3. M.C.M. Attempted micturition by abdominal straining.

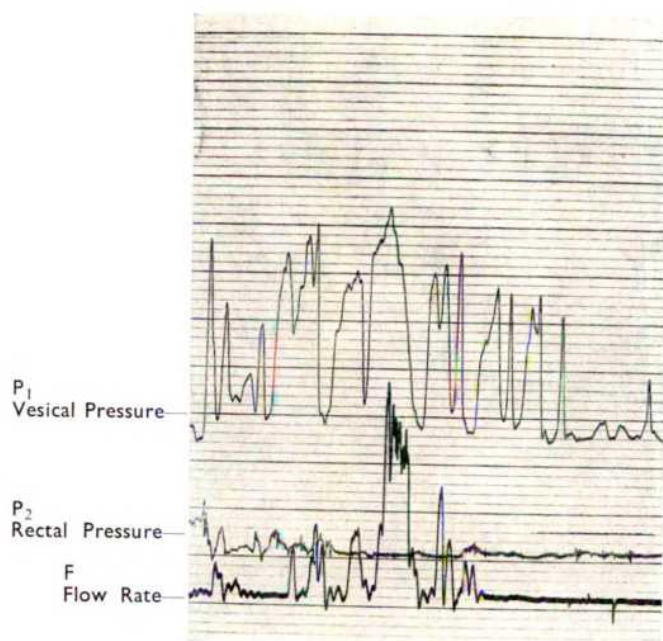


Fig. 4. Case 3. M.C.M. Voiding by straining. P_2 rectal catheter pushed out.

Case 3. J. T. Female, age 37. Following an episode of vesical overdistension in the 8th month of pregnancy, this patient had an 8-year history of persistent frequency, attacks of cystitis, and difficulty of micturition, especially between the infective attacks. Pressure flow studies showed voiding mainly by straining (Figs. 3 and 4), and her symptoms were improved by carbachol.

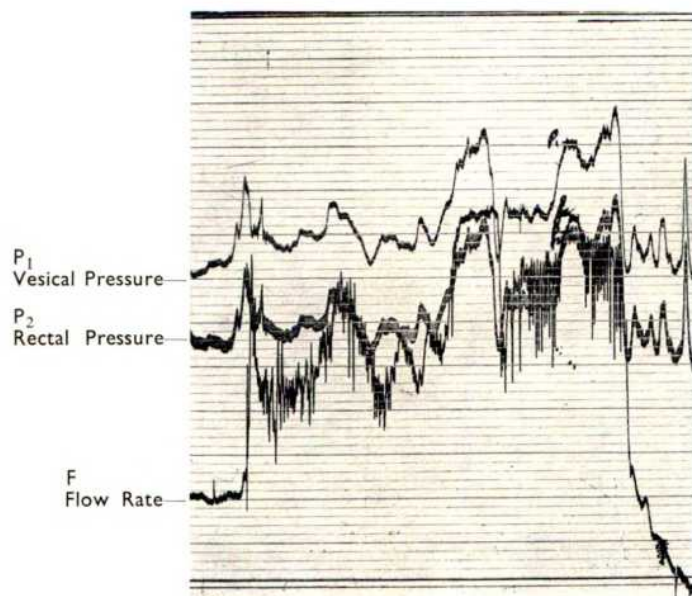


Fig. 5. Case 4. M.C.M. Voiding by straining $P_1 - P_2 = 0$ i.e. No detrusor pressure.

Case 4. J. T. Female, age 50. This patient presented with frequency since the birth of her only child 28 years before. She had almost certainly had a period of overdistension at that time. She had had incontinence for 15 years, initially of the stress variety, and this was temporarily improved by repair of her vaginal prolapse. At the time of her most recent presentation, her incontinence had become total. Pressure flow studies showed a straining pattern of micturition (Fig. 5). Her symptoms were improved by a Marshall–Marchetti operation.

Bladder Biopsies

The biopsies from the 30 patients reported here have been divided into 4 clinical groups (Fig. 6). There were 2 significant abnormalities on electron microscopy. The first was the amount of intercellular collagen which was quantitated arbitrarily as absent (O), slight (+), moderate (++) and heavy (+++). The second feature seen in many of the sections was the variable separation of the individual cells from one another, which in some cases was proportional to the amount of collagen in the intercellular space. In other cases, wide separation could be seen with only moderate or slight deposition of collagen and this separation was attributed to antemortem oedema.

Group I. The neuropathic bladders showed a wide variation in the amount of intercellular collagen. Some biopsies which showed no significant increase in collagen were taken from uninhibited bladders which were heavily trabeculated, and which exhibited grossly abnormal function, while in others a varying amount of collagen was found.

Group II. The bladders from those patients who had few symptoms and only a minor degree of trabeculation had the following ultrastructure appearance. Within the bundles of smooth muscle cells, the cell membranes were closely applied to one another and interdigitated (Figs. 7 and 8).

CLINICAL MATERIAL

Group	No. of Patients
I. Neuropathic	14
II. Slightly trabeculated	7
III. Bladder neck obstruction	5
IV. Overstretched	4
Total	30

Fig. 6.

Collagen fibres were very sparse. At intervals, the plasma membrane showed focal areas of thickening (Fig. 9), due to condensation on the plasma membrane of intracellular fibrils. The resulting electron-dense areas on adjacent cells matched to form intercellular junctions or nexuses. These junctions were closely opposed, but in all there was intervening basement membrane. In some there was an intercellular space within which fine fibrils and occasional collagen fibres were seen. The amount of collagen in Figure 9 was considered pathological.

Group III. In patients with bladder neck obstruction, marked changes were found. In some, moderate (++) intercellular collagen was seen (Fig. 10) and here some of the cell separation was due to autolytic changes. In others, there was gross (+++) intercellular collagen with a comparable amount of cell separation (Fig. 11).

Group IV. The bladders following overdilation showed similar amounts of collagen to those in the obstructed group. The sequence of events following vesical overdilation is illustrated in biopsies taken from Case I. The first, taken 7 days after the overdilation episode when the bladder was still hypotonic, showed antemortem oedema and slight intercellular collagen (Fig. 12). The second, taken from the bladder 2 months later, showed the amount of collagen had increased and cell separation was then proportional to the amount of collagen in the intercellular space (Fig. 13).

The assessment of intercellular collagen in the 30 cases examined is shown in Figure 14. In none of the sections examined by light microscopy was there any evidence of inflammatory cells in the muscle layer of the bladder wall.

Discussion

Overdistension of the bladder in man can produce severe functional changes. In the rabbit, a single overstretch episode can stimulate the formation of intercellular collagen, a finding that is absent in normal controls.

Normal human bladder biopsies, and in particular those from adolescent bladders, have been difficult to obtain. We thought it unjustifiable to biopsy completely normal bladders, and patients having cystoscopies or open bladder operations usually have micturition symptoms or infection with concomitant bladder abnormalities.



Fig. 7



Fig. 8



Fig. 9

Fig. 7. Cells interdigitate. Sparse collagen fibres. $\times 2,000$.

Fig. 8. Cell membranes closely applied. $\times 10,000$.

Fig. 9. Focal thickening on intercellular fibrils on plasma membrane. Slight cell separation with intervening collagen fibrils. $\times 10,000$.



Fig. 10. Moderate ++ intercellular collagen. Cell separation partly artefactual. $\times 2,000$.



Fig. 11. Severe +++ intercellular collagen with cell separation. $\times 2,000$.

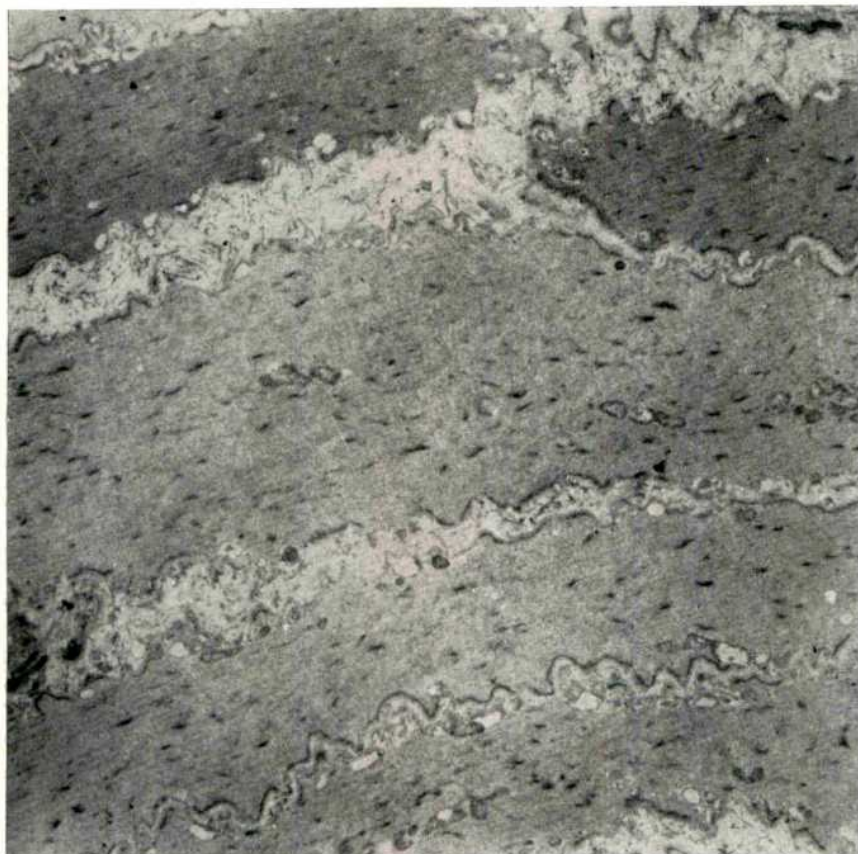


Fig. 12. Case 1. Vesical biopsy 7 days after overstretch. Oedema separates cells. $\times 2,000$.

In the human detrusor, intercellular collagen has been found in a variety of conditions, but the amount seems to be proportional to the severity of the original insult to the bladder. The exception to this seems to be in neuropathic bladders where there is marked variation with some severely disordered and trabeculated bladders showing scanty intercellular collagen. In the overstretched bladder, it seems possible that the intercellular junctions or nexuses are interrupted. There is considerable evidence that excitation transmission in smooth muscle is from muscle cell to muscle cell via these nexuses (Dewey, 1965). In the two cases of overstretching investigated in the acute phase, paralysis of the detrusor ensued. Recovery occurred after 3 weeks in 1, but in the other 1 and the 2 who presented some years later, there was little evidence of detrusor activity, and voiding was accomplished by abdominal straining.

All these women had overdistension episodes associated with pregnancy and delivery, and it may be that the detrusor is more liable to damage in this clinical situation. Certainly it is probable that the female bladder is more susceptible to damage because of the relative thinness of its wall.

It is suggested that, following overstretching, the nexuses are interrupted with only temporary loss of function in most cases, but in a few the bladder remains hypotonic. Intercellular collagen deposition may occur as a result of this intercellular disruption, and may in part be responsible for the continuing loss of excitation transmission in those patients whose bladders do not recover. The stimulus for intercellular collagen formation in the other conditions may be related to overdistension episodes which sometimes occur during the course of any bladder disorder.

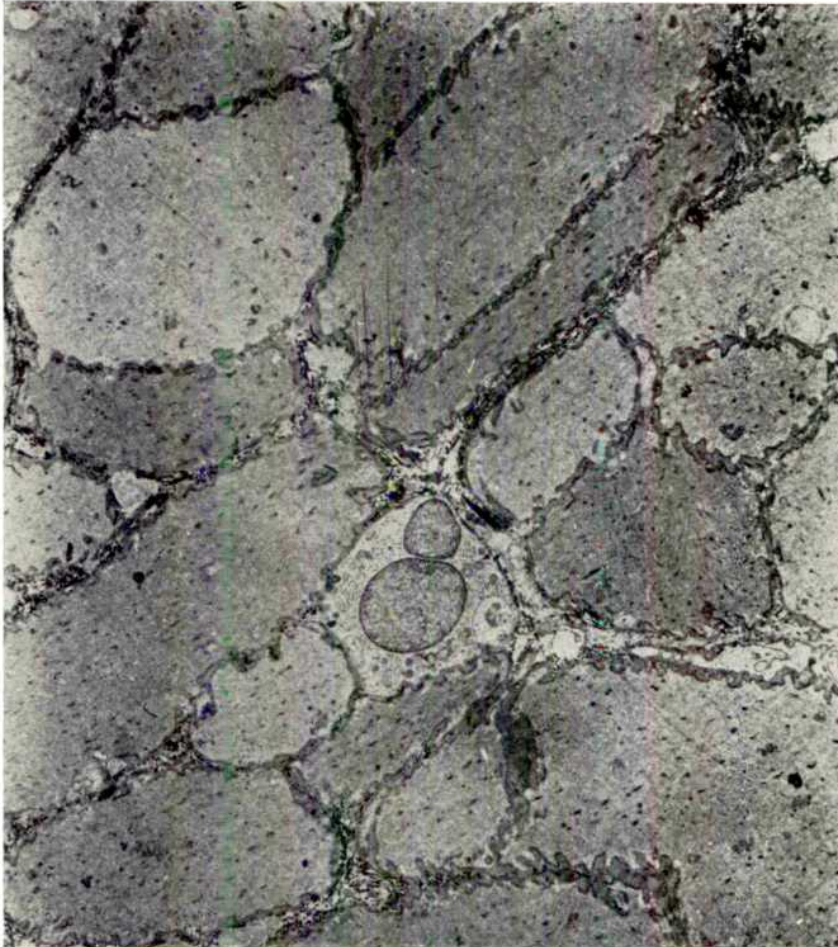


Fig. 13. Case 1. Vesical biopsy 2 months after overstretch. Collagen present between separated cells. $\times 2,000$.

Inflammatory cells were absent in all the specimens examined, which makes infection an unlikely explanation of this phenomenon.

It is difficult to say at the moment whether electron microscopy of the bladder will have any clinical application. The formation of intercellular collagen may be a very non-specific response to a variety of insults. What is surprising is that some bladders work so well with heavy collagen deposition and others look relatively normal but function so poorly.

Summary

Studies in 30 patients with vesical lesions show that intercellular collagen is present in varying amounts. Pressure flow studies in 4 patients who had undergone vesical overdistension episodes showed full recovery in only 1 patient, with straining micturition in the other 3. In all 4, marked intercellular collagen was found in the bladder biopsies. These changes are similar to those found in the experimental model.

This work was supported by a grant from the Multiple Sclerosis Society, to whom we are most grateful.

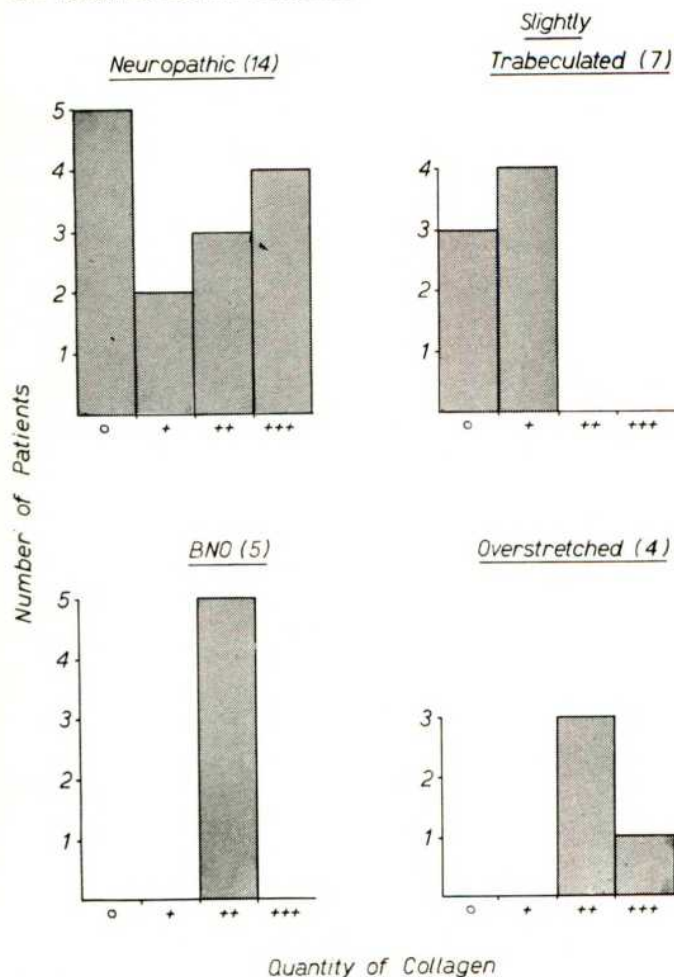


Fig. 14.

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Genital Reconstruction in the Female with the Adrenogenital Syndrome¹

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In the infant with ambiguous external genitalia secondary to adrenocortical hyperplasia, after the sex has been established unequivocally as female, and after appropriate substitution therapy has controlled the electrolyte and hormonal aberrations, the problem of revision of the external genitalia arises. The dual objectives are a satisfactory cosmetic appearance and future functional capability. To these ends the urogenital sinus must be converted into a normal vaginal outlet and the hypertrophied clitoris must be disposed of in some fashion.

In the past we were content simply to do an amputation of the clitoris flush with the symphysis, along with a midline posterior episiotomy, to make the vaginal outlet. The appearance of the external genitalia in girls so treated was improved but left much to be desired, and more importantly the vaginal orifice had a great tendency to show cicatricial contraction requiring repeated digital dilations for prolonged periods of time.

We have achieved distinctly improved results using the techniques described herein. In essence, the urogenital sinus is converted into an appropriate vaginal orifice utilising the VY-plasty principle and a subcutaneous amputation of the shaft and crura of the clitoris is performed, retaining the glans. It is helpful to demonstrate this interrelationship of urethra, vagina and urogenital sinus both by voiding cystourethrography and by panendoscopy prior to operation.

Introitoplasty

Under general anaesthesia with the patient in the exaggerated lithotomy position, an inverted V incision is made with the apex of the V at the posterior aspect of the opening of the urogenital sinus (Fig. 1, A). This point is referred to as *a*. Each limb of the V extends backward to a point midway between ischial tuberosity and anus, much as in a perineal prostatectomy. The flap proper is dissected backward to its base and the lateral margins of the incision are undermined widely.

An incision is then made along the floor of the urogenital sinus from the initial point *a* proximally until the separate orifices of the urethra and vagina are seen clearly (Fig. 1, B and C). This incision, which is often several centimetres in length, may be regarded as the stem of a Y whose proximal point is designated *a'*. The overlying tissues, including the perineal body, are likewise incised making in effect a midline episiotomy. A Foley catheter is now passed through the urethra to the bladder.

The V flap is next positioned in the midline episiotomy as an inlay and its apex *a* is sutured to *a'* with fine catgut sutures (Fig. 1, D). Careful approximation of skin to mucosal surface, avoiding raw edges which could give rise to granulations and adhesions, is critical if subsequent stricture is to be avoided. The adjacent margins of the wound are then closed as indicated in the drawings (Fig. 1, E).

¹Read at the Twenty-eighth Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

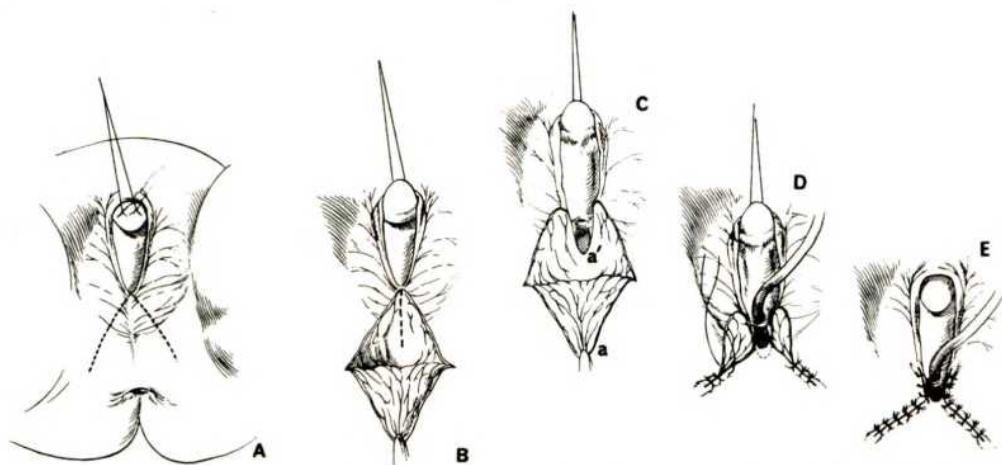


Fig. 1. Technique of vaginoplasty. A, Outline of skin flap. B, Incision of urogenital sinus. C, Urethral and vaginal orifices exposed. D, Skin flap sutured into depth of urogenital sinus. E, Final result.

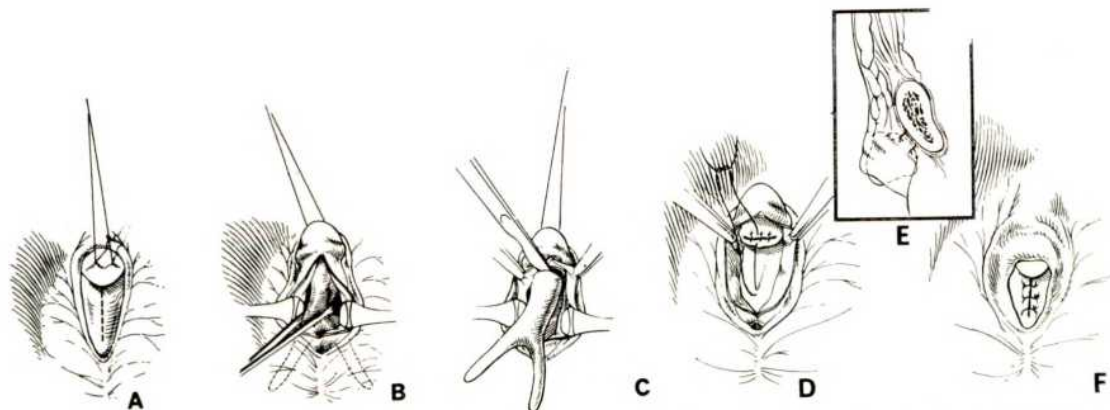


Fig. 2. Technique of clitoroplasty. A, Outline of incision on ventral surface of shaft. B, Mobilizing shaft of clitoris. C, Excision of clitoral shaft, preserving glans. D, Suturing stump of glans to undersurface of pubis. E, Final result, side view. F, Final result, frontal view.

Clitoroplasty

Clitoroplasty may be done at the same time as the vaginoplasty or as a separate procedure. The principle utilised is a subcutaneous amputation of the shaft of the clitoris, including the crura, but sparing the glans. Initially, we approached the shaft through a ventral longitudinal incision (Fig. 2, A), mobilising it down to its attachments to the inner aspect of the pubic arch and up to the base of the glans (Fig. 2, B). The entire shaft was then excised (Fig. 2, C), and haemostasis of the stumps secured by means of suture ligation, leaving the glans attached to its hooded prepuce. The base of the glans was sutured to the lower edge of the pubic symphysis (Fig. 2, D and E) following which the mucosal incision was closed (Fig. 2, F).

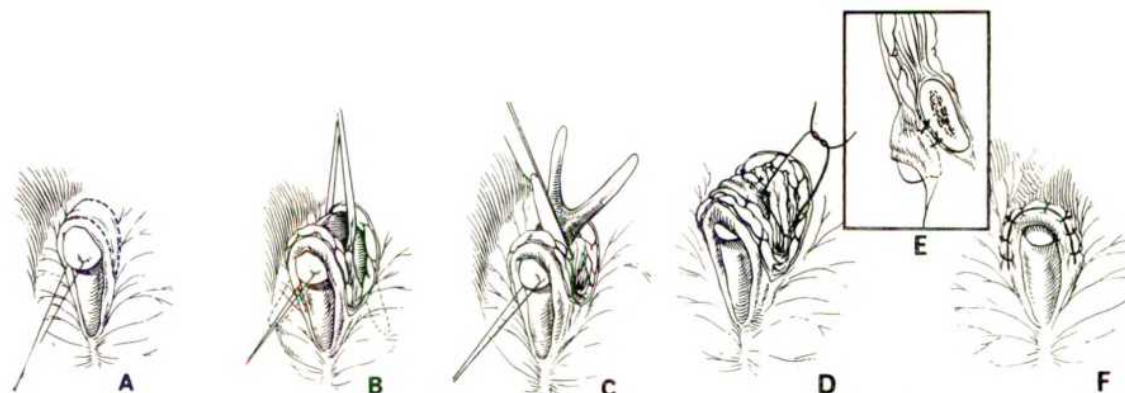


Fig. 3. Clitoroplasty, alternative technique. A, Outline of incision over dorsum of shaft. B, Mobilisation of shaft. C, Excision of shaft. D, Suturing stump of glans to undersurface of pubis. E, Final result, side view. F, Final result, frontal view.

This approach proved to be technically satisfactory but there still remained considerable redundancy of the foreskin and recently the operation has been modified with some improvement cosmetically. The shaft is now approached posteriorly after first wedging out the redundant foreskin (Fig. 3, A and B). As before, the entire shaft, exclusive of the glans, is excised (Fig. 3, C) and the base of the glans is once more sutured to the inferior edge of the pubic symphysis (Fig. 3, D, E and F).

With either approach, the primary blood supply to the glans is interrupted and it must now depend upon soft-tissue collaterals for survival. To date, this has proved adequate since none has sloughed but admittedly the glans is somewhat dusky in colour for several days after the procedure. An unexpected dividend from this state of transient ischaemia, however, has been some degree of atrophy and shrinkage, reducing the glans to a size more consistent with that of the normal female clitoris.

Discussion

The presence of ambiguous genitalia in a child is a continuing source of anxiety to the family even after the sex of the child has been established firmly. Hence it is incumbent upon the attending physician to resolve this issue as soon as practicable. We agree with Money and the Hampsons (1955) that early definitive correction prior to the age of permanent memory is most desirable for the child, while promoting a healthy parental attitude as well. The actual age at which operation

is undertaken obviously is dependent upon a stable metabolic and hormonal state in the infant, but it is usually safe to proceed with reconstruction at 1 year of age and probably sooner.

Definitive reconstruction is less urgent perhaps as far as the urogenital sinus is concerned since this aspect of the deformity is less apparent to the casual observer than is that of the enlarged phallus. There is, in fact, some justification for postponing the vaginoplasty until the child is older in the hope of lessening the possibility of stricture at the repair site. In this regard the sliding-flap principle introduced by Fortunoff *et al.* (1964) and employed by us to reconstruct the urogenital sinus has proved superior to simple midline incision. It is adequate cosmetically and functionally except perhaps for those rare completely masculinised individuals with a penile urethra and high vaginal termination who may require a more elaborate approach such as that described by Hendren and Crawford (1969).

There seems, however, little to be gained by undue delay in performing the clitoroplasty. We have never personally observed regression in size of this structure even under good medical management. On the contrary, it has been the experience of most observers that the size of the clitoris parallels the growth of the child. It seems, therefore, that if the size, appearance, projection and erectile tendency of the organ constantly challenge the assigned sex at every diaper change, specific treatment is in order. Possession of a clitoris is not essential for orgasm in the female (Randolph and Hung, 1970) and one need not hesitate unduly to remove it if a useful purpose is thereby served. The objective thus becomes one of selection of the technique which results in an appearance most closely approximating the normal. Until recently the procedure most commonly employed was that of total amputation (Gross, Randolph and Crigler, 1966), although Lattimer (1961) and Randolph and Hung (1970) described relocation and recession of the clitoris as an alternative. This latter procedure may successfully hide the organ from view, but we cannot help but feel that the sheer bulk of the tissue involved with its retained sensitivity and tendency to engorgement may be a serious shortcoming of this approach.

We have now carried out genital reconstruction as described above in two infants and one 19-year-old girl with the adrenogenital syndrome. In all, the appearance of the external genitalia following vaginoplasty and clitoroplasty has closely approximated the normal. The experience of Goodwin (1969) confirms the favourable outcome which may be expected when appropriate surgical procedures are applied to this distressing problem.

Summary

Operative procedures for the correction of ambiguous external genitalia in girls with the adrenogenital syndrome are described. Reconstruction of the vaginal aperture utilises the VY principle, while the hypertrophied clitoris is managed by amputation of its shaft and crura in a subcutaneous manner preserving the glans. Results in 3 cases have been satisfactory, leading us to recommend these methods for further trial.

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The Effect of Progesterone on the Adrenergic Receptors of the Urethra¹

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There has been considerable interest in recent years in the possible beneficial effect of progesterone derivatives in the treatment of benign prostatic obstruction, and there appears to be gradually accumulating evidence that in some patients at least, a certain degree of relief of their symptoms does occur on administration of these compounds. It is generally automatically assumed that any effect produced is hormonal in nature, but a chance observation has led us to query whether this is necessarily entirely so. During the trial of a locally produced progestational agent, we noted that a few reliable patients reported an improvement in symptoms within a day or two of starting the drug, instead of after a more prolonged period, as would be expected with a hormonally acting compound. This observation was made at about the same time as we were investigating the actions of oestrogen and progesterone on the ureter, as a result of which we found evidence of a pharmacological action of these hormones on the adrenergic receptors in the ureter (Raz *et al.*, 1972*b*). The coincidence of these two observations, together with the fact that both we (Raz and Caine, 1972; Raz *et al.*, 1972*a*) and other workers (Tanagho *et al.*, 1969) had demonstrated the presence of adrenergic receptors in the urethra, led us to investigate whether in the urethra, also, progesterone had a comparable effect on the adrenergic receptors.

Materials and Methods

A series of 32 sets of experiments was performed on mongrel female dogs, weighing from 8 to 12 kg each, using a similar technique to that we employed in demonstrating the presence of α - and β -adrenergic receptors in the ureter. The dogs were anaesthetised with intravenous pentobarbitone, and the various drugs examined were administered intravenously. Urethral pressure profile studies were performed by the technique described by Brown and Wickham (1969), the special catheter being connected via a Sanborn pressure transducer to a Sanborn recorder. The catheter was slowly withdrawn along the urethra at a steady rate by mechanical means, and the recording of the pressure profile made at a paper speed of 10 mm/sec, and a sensitivity of 10 mm pen deflection per 10 mm mercury pressure. The urethral pressure responses to various adrenergic stimulating and blocking agents, both before and after the administration of progesterone, were examined by this technique.

Results

Administration of a small dose of noradrenaline (50 γ) intravenously resulted in an increase in the intra-urethral pressure (Fig. 1). As previously demonstrated, this is an expression of the predominantly α -adrenergic stimulating effect of the noradrenaline, which overshadows its mild

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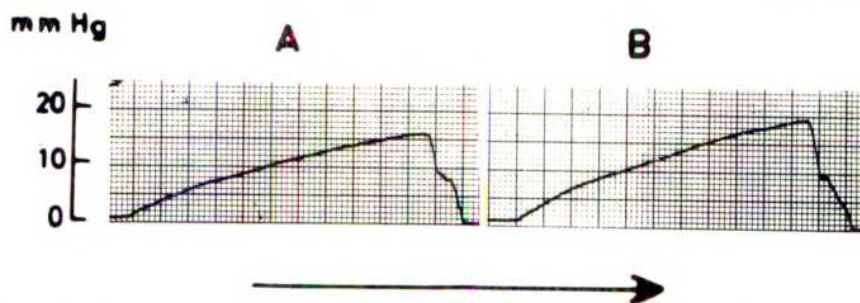


Fig. 1. Urethral pressure profile response to noradrenaline. A, control. B, increased intra-urethral pressure following administration of noradrenaline.

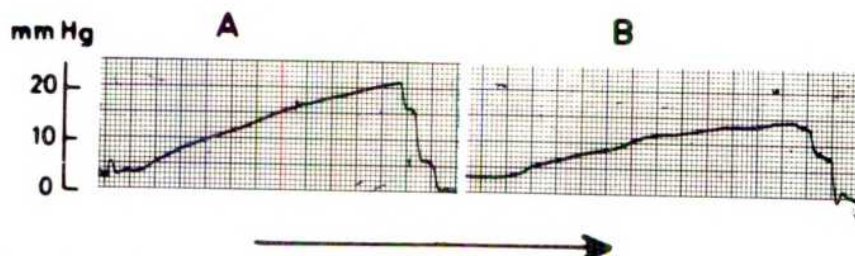


Fig. 2. Response to noradrenaline following pre-treatment with progesterone. Same dog and dosage as in Figure 1. A, control. B, decreased intra-urethral pressure following administration of noradrenaline.

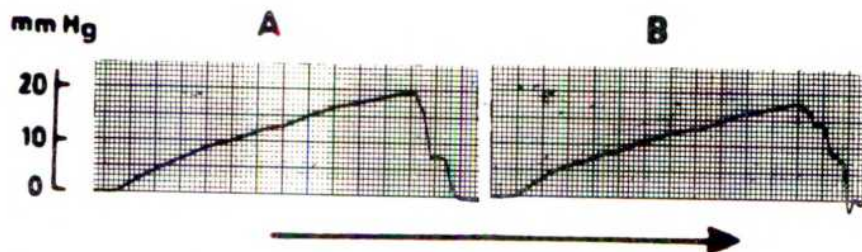


Fig. 3. Response to Isuprel. A, control. B, minimal decrease in intra-urethral pressure following administration of Isuprel.

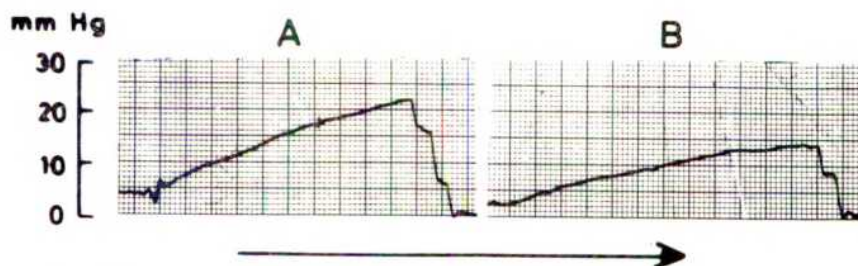


Fig. 4. Response to Isuprel following pre-treatment with progesterone. Same dog and dosage as in Figure 3. A, control. B, enhanced decrease in intra-urethral pressure following administration of Isuprel.

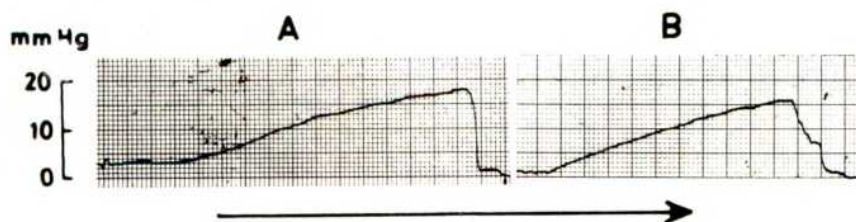


Fig. 5. Response to Regitine. A, control. B, decreased intra-urethral pressure following administration of Regitine.

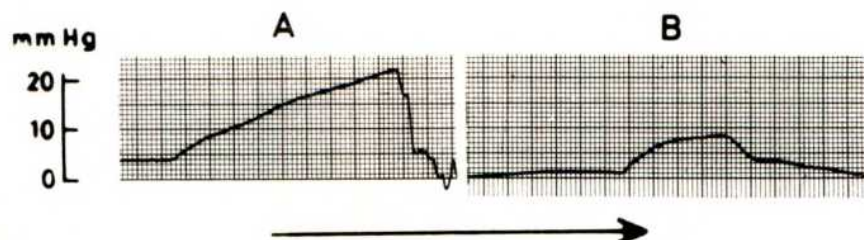


Fig. 6. Response to Regitine following pre-treatment with progesterone. Same dog and dosage as in Figure 5. A, control. B, enhanced decrease in intra-urethral pressure following administration of Regitine.

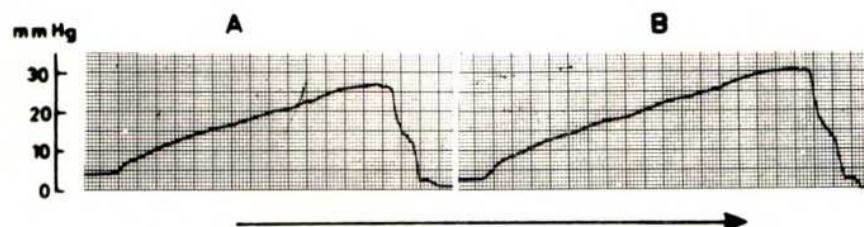


Fig. 7. Response to Inderal. A, control. B, increased intra-urethral pressure following administration of Inderal.

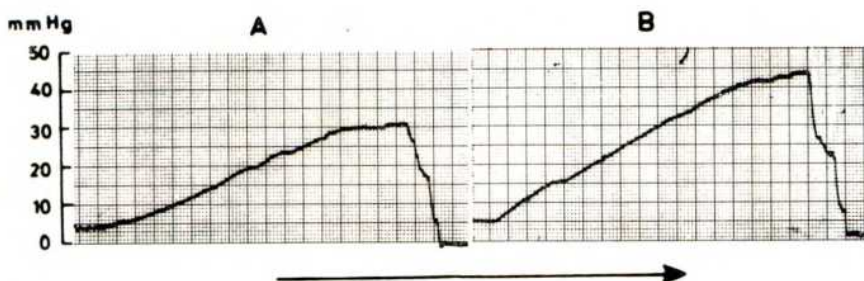


Fig. 8. Response to Inderal following pre-treatment with progesterone. Same dog and dosage as in Figure 7. A, control. B, Enhanced increase in intra-urethral pressure following administration of Inderal.

β -adrenergic effect. The dogs now received treatment consisting of 50 mg progesterone (Ayerst) by injection daily for 3 days, and the experiment was repeated. Following this pre-treatment, the response to the same quantity of noradrenaline was reversed, and in all cases there was a reduction of intra-urethral pressure instead of an increase, revealing a predominantly β -response (Fig. 2).

Isuprel (isoproterenol) is a β -adrenergic stimulator, and its administration in an effective dose causes a drop in intra-urethral pressure. However, a single intravenous dose of 15 γ was subliminal in the majority of the dogs tested, and produced practically no change in the urethral pressure profile (Fig. 3). Following treatment as described with progesterone, the administration of the same quantity of Isuprel now produced a clear β -effect, with a fall in the urethral pressure recording (Fig. 4).

Regitine (phentolamine) in a dose of 3 mg intravenously produce a fall in the intra-urethral pressure due to blocking of the α -adrenergic receptors (Fig. 5). Following the pre-treatment with progesterone, the same dose of Regitine now produced a more pronounced drop in pressure (Fig. 6).

Inderal (propranolol) is a β -adrenergic blocker and administration of 1 mg intravenously was sufficient to cause a mild rise in the intra-urethral pressure because of this effect (Fig. 7). Following the pre-treatment with progesterone, administration of the same quantity of Inderal now produced a much more pronounced rise in the intra-urethral pressure (Fig. 8).

Discussion

As mentioned above, both we and other workers have demonstrated the presence of α - and β -adrenergic receptors in the urethra, α -receptor stimulation causing an increase in the tone of the urethral smooth muscle and hence in the intra-urethral closure pressure, β -receptor stimulation having the opposite effect. It is evident from the above series of experiments that the administration of progesterone produces an effect on the adrenergic receptor response of the urethra, in some instances increasing it and in others reversing it. The nature of the effects observed above can best be explained by postulating that the progesterone has an enhancing or facilitating effect upon the β -receptors. Thus, in the case of noradrenaline administration, the enhancement of the β -receptors results in the relatively small β -effect becoming preponderant, instead of the usual α -preponderance. In the case of Isuprel, the normal β -effect is much increased, and a small dose which was previously almost ineffective, produces a marked response following progesterone treatment. Further confirmation can be adduced from its effects upon the adrenergic blockers. Regitine, by blocking the α -component of the resting urethral pressure, leaves the β -component predominant and hence produces a drop in urethral pressure. Following progesterone, this β -component is enhanced, and thus the fall in pressure is greater. Finally, administration of Inderal has the opposite action, and blocks the β -receptors, thus resulting in an increased intra-urethral pressure due to the unopposed α -receptors. Following the pre-treatment with progesterone, it is suggested that the β -component in the resting urethral pressure is enhanced and therefore following its block with Inderal there is now a correspondingly greater increase in pressure.

The results obtained here are comparable to those we obtained when investigating the effect of oestrogen and progesterone on the ureter. As pointed out there, although the exact mechanism of the effect of the female hormones on the adrenergic receptors is not clear, it is probably the same mechanism as occurs in the "pregnancy reversal" described as long ago as 1906 by Dale. In that year, both he and Cushny described a change in the reaction to hypogastric nerve stimulation or the intravenous injection of adrenaline, of the pregnant as opposed to the virgin cat uterus. The change has subsequently been shown to depend on the altered hormonal environment, and this in turn has been shown to produce its effect by changing the relative dominance of the adrenergic receptors (Raz *et al.*, 1971).

There is evidence that the β -receptors, and possibly also the α -receptors, are closely related to adenyl cyclase, or may even be identical with it. This substance catalyses adenosine triphosphate

(ATP) to cyclic adenosine monophosphate (AMP) upon the level of which many of the cellular processes depend (Robinson *et al.*, 1967). The actual effects produced by the adrenergic agents appear to depend upon a shift of electrolyte across the cell membranes, and this may be due to changes in the calcium binding of the muscle membrane (Bulbring and Tomita, 1968). Thus, α -adrenergic actuation is associated with sodium influx and potassium and chloride outflow from the cell, which results in depolarisation and activation of muscle contraction. β -adrenergic stimulation is associated with the opposite electrolyte shift, resulting in membrane hyperpolarisation and inhibition of muscle activity. It has been shown that progesterone administration results in electrolyte shift similar to that produced by β -adrenergic agents, and it may therefore be this complementary action on the electrolytes that facilitates or enhances the response of the muscle cells.

Whether or not this explanation ultimately proves to be the correct one, the experimental results described above indicate that the progesterone has a pharmacological action upon the adrenergic receptors in the urethra, consisting of an enhancement of the β -adrenergic response. It is suggested that this action may to some extent explain the beneficial effect produced on some patients with obstructive prostatic symptoms.

Summary

A series of urethral pressure profile studies was performed on dogs, to investigate the effect of pre-treatment with progesterone on the adrenergic responses.

The results obtained indicate that progesterone facilitates or enhances the β -adrenergic response. The possible mechanism by which this effect is produced is discussed.

It is suggested that this modification of the adrenergic response of the urethra may partly explain the beneficial results reported in prostatic obstruction.

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Treatment of Patients with Calcium-containing Renal Stones with Cellulose Phosphate

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The occurrence of urinary tract stones and their location has a characteristic geographical distribution. There are many areas of endemic bladder stone disease, mainly in underdeveloped countries such as India, Pakistan and Africa, the stones being composed chiefly of ammonium hydrogen urate and calcium oxalate, which tend to disappear with technological progress and rising standards of living. On the other hand, in the European countries with developed technology, as also in the USA, calcium-containing stones of the upper urinary tract are predominant (Cygan *et al.*, 1959; Prien and Prien, 1968; Zieliński, 1954).

An essential condition for the formation of renal stone, regardless of its chemical composition most probably is an oversaturation of urine with the stone constituents.

The deciding factor for oversaturation with regard to brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) is hypercalciuria, whereas of minor importance is a persistent alkaline urinary pH; with regard to weddellite (calcium oxalate dihydrate) the corresponding factors are urinary calcium and oxalate excretion (Hodgkinson *et al.*, 1971). In any case, the increased urinary calcium is a common risk factor in both the most frequent types of calcium-containing stones.

There are now a number of ways of reducing high urinary calcium. High fluid intake may be recommended for all stone-formers as a basic protective means. A diet with a very low calcium content—less than 50 mg daily—should provide an effective method of reducing calciuria (Keynes *et al.*, 1971), but due to the presence of calcium in so many kinds of food and in drinking water, such a diet is hardly possible. It is not palatable, and would lack many indispensable trace elements. In such a situation, cellulose phosphate—which has a particular affinity for calcium and forms an inabsorbable complex—seems to be the drug of choice in the treatment of hypercalciuria (Dent *et al.*, 1964; Parfitt *et al.*, 1964; Pak *et al.*, 1971; Rapado *et al.*, 1970). This paper reports the effects of treatment of 13 patients with sodium cellulose phosphate (SCP)—a proven calcium binding agent.

Material and Methods

The essential clinical data are shown in Table I. Two patients with primary hyperparathyroidism were treated with SCP while awaiting investigation to identify the site of the adenoma. A further 2 patients with recurrent renal stones, normocalciuria and incomplete renal tubular acidosis of distal type (urine pH after 130 mEq of ammonium chloride over 5.5), and 2 patients with hyperoxaluria were treated.

The definition of hypercalciuria should be adjusted for dietary calcium during investigation (Peacock *et al.*, 1967). As our standard hospital diet supplies about 450 mg calcium per day, urinary calcium excretion exceeding 200 mg was considered to be abnormally high in in-patients, whereas 300 mg were regarded to be the upper normal limit in out-patients. According to these criteria about 5 per cent of normal patients and 60 per cent of stone-formers have hypercalciuria

(Parfitt *et al.*, 1964; Peacock *et al.*, 1967; Epstein, 1968; Kollwitz *et al.*, 1969). In some of these patients the specific cause of existing hypercalciuria can be found, but in most cases none of the known causes can be established, which justifies the temporary diagnosis of idiopathic hypercalciuria.

After the establishment of the clinical diagnosis, at least 2 basal 24-hour urine collections were analysed for calcium, phosphorus, oxalate and creatinine. SCP was administered, usually in a dose of 15 g per day, the patients being instructed to avoid excessive amounts of foods known to have a high calcium content. The patients were seen at least bimonthly in the Nephrology Out-Patient Clinic.

Estimations of the non-protein nitrogen, creatinine, sodium, potassium, chloride, calcium, phosphorus, aminotransferases, alkaline phosphatase (with heat stability test), liver function tests and blood morphologic examinations were performed by the standard laboratory methods published by Kokot (1969).

The patients were instructed to collect urine carefully during 24 hours. This was analysed for calcium, inorganic phosphorus, creatinine and oxalic acid as described by Dick (1967). Magnesium, copper and zinc serum concentrations were determined by means of atomic absorption spectrophotometry (Unicam SP-90).

Results

In all 13 patients under treatment we found significant reduction of the urinary calcium excretion to less than 50 per cent of basal values. No patient exhibited calcium excretion exceeding 200 mg per day on long-term treatment in spite of having their usual diet (Fig. 1). Attacks of renal colic and the passage of small stones, often occurring in the antecedent months or years, became less frequent (Table II). In both patients with primary hyperparathyroidism we also observed improvement in the symptoms and sequelae of the hypercalcaemia: headaches, nausea, irritability and hypertension (Fig. 2). We have not observed any subjective side-effects of long-term treatment: renal function, blood cells, serum electrolytes, liver function tests, aminotransferase and serum alkaline phosphatase activities did not show any significant changes during continued treatment with cellulose phosphate in a dose of 5 g thrice daily.

From the theoretical point of view the binding of other metals which could lead to trace-metal deficiencies could be expected, especially in the course of prolonged treatment of hypercalciuria. Therefore, the sera of patients included in this controlled programme were analysed bimonthly for magnesium, iron, copper and zinc concentration, by means of atomic absorption spectrophotometry (Fig. 3, Table III). In 4 patients we observed low serum magnesium concentration under 1.6 mg per 100 ml in the course of therapy (Fig. 3). Although there was a general trend for lower iron, copper and zinc serum concentrations, statistical analysis did not confirm significance of those differences at a 5 per cent probability value (Table III).

Discussion

The metabolic studies by Dent *et al.* (1964), Parfitt *et al.* (1964), Rapado *et al.* (1970) showed increased intestinal calcium absorption in patients with hypercalciuria although it was not possible to exclude primary renal calcium loss in some of them. Among hypotheses concerning the cause of idiopathic hypercalciuria, normocalcaemic primary hyperparathyroidism (Rapado, 1970) and high carbohydrate consumption have been proposed (Lemann *et al.*, 1969). Recently it was shown by Reddy (1971) that germfree animals have enhanced intestinal absorption and urinary excretion of calcium and magnesium. This finding could be of interest if compared with significant consumption of sterilised food in technologically developed countries.

No useful method for diminishing hyperoxaluria has been found so far, although Dent and Stamp (1970) tested several substances for this purpose. Since Zarembski and Hodgkinson (1969)

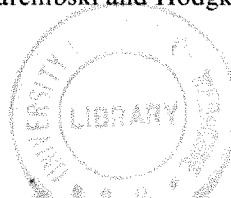


Table I

Essential Clinical Data of Patients before Treatment with Sodium Cellulose Phosphate.

Patient	Sex	Age	U _{Ca}	U _{ox}	Stones	Abnor- mal Bones	C _{inul}	Max. S.G.	Min. pH	Clinical Diagnosis
1. W. T.	F	46	345	4	—	+	122	1016	6.0	Primary hyperpara- thyroidism
2. Go. W.	M	26	276	16	+	+	70§	1023	6.1	Primary hyperpara- thyroidism. Bilateral stag- horn calculi
3. K. Z.	M	29	352	—	+	—	87	1025	5.3	Medullary sponge kidney. Nephrocalcinosis
4. W. K.	F	45	381	16	+	—	103	1028	4.6	Idiopathic hypercalciuria. Right staghorn calculus
5. K. J.	M	45	354	—	+	—	75	1022	5.1	Idiopathic hypercalciuria
6. K. K.	F	35	420	59	+	—	62	1022	—	Idiopathic hypercalciuria
7. Gr. W.	M	32	266	60	+	—	110§	1021	4.8	Idiopathic hypercalciuria
8. D. S.	M	37	300	75	+	—	102§	1024	—	Idiopathic hypercalciuria
9. G. J.	M	27	202	—	+	—	81§	1026	5.4	Idiopathic hypercalciuria
10. P. M.	F	58	97	8	+	+	47§	1010	6.5	Staghorn calculi. Osteo- porosis
11. B. A.	F	42	94	24	+	—	62	1016	5.6	Staghorn calculi
12. W. E.	F	20	102	46	—	—	98§	1026	—	Haematuria. Hyper- oxaluria
13. K. Z.	M	17	115	81	—	—	160§	1026	4.6	Haematuria. Hyper- oxaluria. Vit. K deficiency

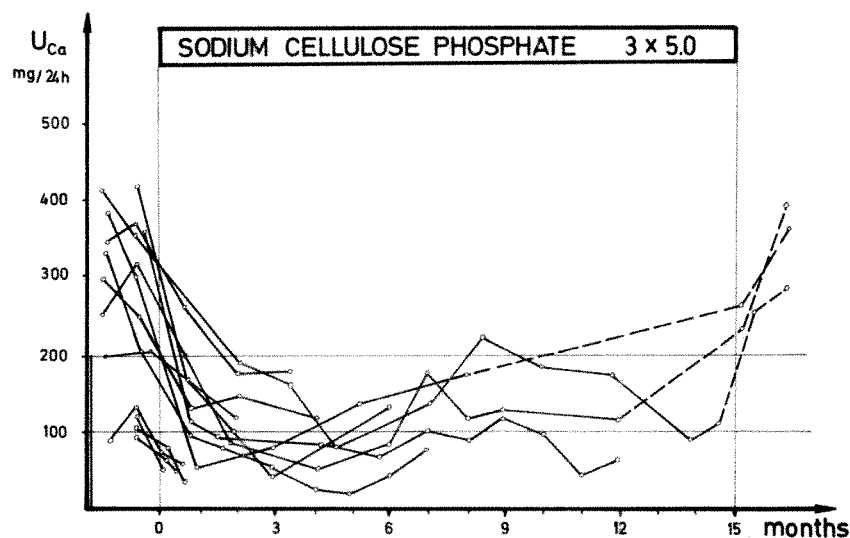
U_{Ca} 24 hours' urinary calcium expressed in mg/24 h.U_{ox} —24 hours' urinary oxalic acid excretion (upper normal limit = 35 mg/24 h).C_{inul}—Clearance of inulin or creatinine (§).

Fig. 1. Urinary calcium excretion in follow-up patients.

Table II

The Occurrence of Renal Colic and Passage of Stones in the Course of Treatment with Sodium Cellulose Phosphate

	Total Period of Observation (months)	Stones	Renal Colics (without stone)	Mean Monthly Occurrence	
				Stones	Colics
Basal	147	29	42	0.197	0.286
On cellulose phosphate	51	3	11	0.059	0.216

This table was based on the clinical data of 7 patients who passed at least 1 stone during 6 months or longer of basal and therapeutic follow-up, *i.e.* Go. W., W. K., K. J., K. K., Gr. W., D. S., G. J.

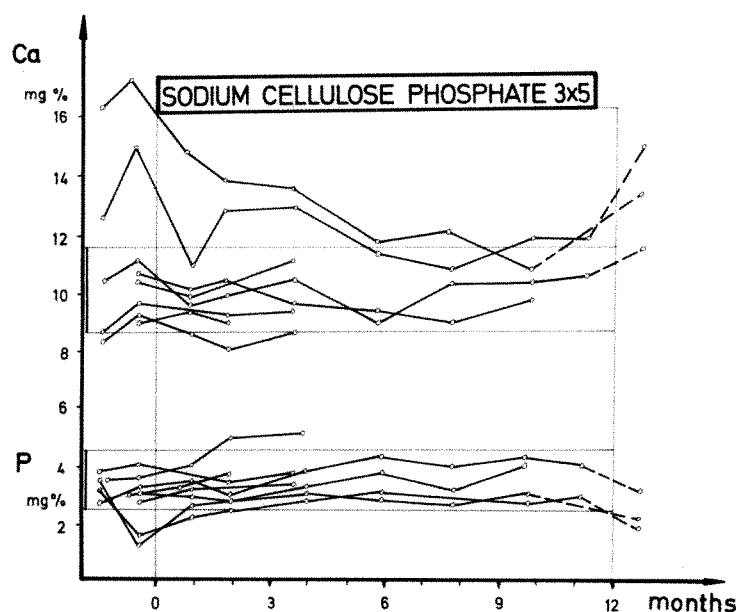


Fig. 2. Serum calcium and inorganic phosphorus concentrations in follow-up patients.

reported that in many patients urinary oxalate excretion parallels that of calcium, we have tried to evaluate the effect of cellulose phosphate on oxaluria. Of 10 patients studied, 4 showed lower urinary oxalate values during cellulose phosphate treatment, in 1, constantly low values, but in the remaining 5 patients, we found higher quantities (Fig. 4). Figure 5 suggests but does not prove the existence of a hyperbolic relation between urinary oxalic acid and calcium excretion. We cannot draw any conclusion on the effect of cellulose phosphate on urinary oxalate from these divergent results. However, since there are no other effective means of controlling hyperoxaluria, a further trial of treatment to control hyperoxaluria might be of interest; particularly as long-term treatment with cellulose phosphate has hardly any adverse side-effects.

Increased urinary oxalic acid excretion was observed mainly in patients who developed hypomagnesaemia (Fig. 4) and who displayed a fall in urinary calcium excretion to below 100 mg per

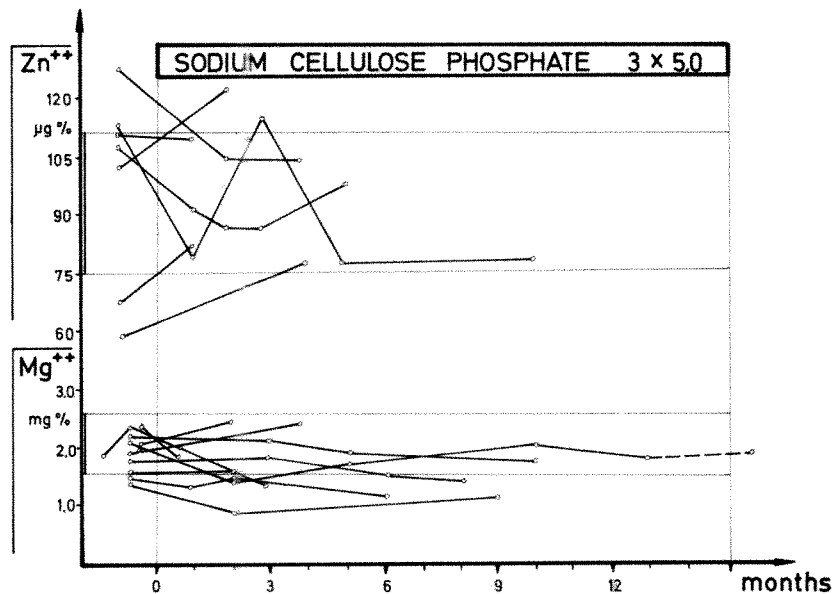


Fig. 3. Serum zinc and magnesium concentrations in follow-up patients.

Table III

Effects of Cellulose Phosphate on Serum Ca, P, Mg, Zn, Fe, Cu and Urinary Excretion of Ca, P and Oxalic Acid

Parameter		Mean Values		t	p
		Basal	On SCP		
Serum:					
Ca	mg/100 ml	10.35	9.92	1.18	NS
P	mg/100 ml	3.42	3.71	1.51	NS
Mg	mg/100 ml	1.93	1.73	1.38	NS
Zn	µg/100 ml	110.7	100.7	0.93	NS
Fe	µg/100 ml	113.4	98.9	1.43	NS
Cu	µg/100 ml	103.7	92.7	0.66	NS
Urine:					
Ca	mg/24 h	252.0	110.1	5.31	<0.001
P	mg/24 h	811.6	941.4	1.30	NS
Oxalic acid	mg/24 h	38.7	46.1	0.64	NS

day (Fig. 5). Both correlation coefficients, urinary oxalate versus serum Mg, and log urinary oxalate versus log urinary calcium were consistent with a weak but significant relation. As 15 g of SCP has a capacity to bind about 52 mEq of divalent cations (= 1,000 mg Ca), the patients ingesting less than that amount of calcium would saturate only a part of phosphate groups, and the unsaturated valencies would combine with Mg forming inabsorbable complexes. According to Sutton (1968) the hypomagnesaemia due to this hypothetical mechanism could be corrected by

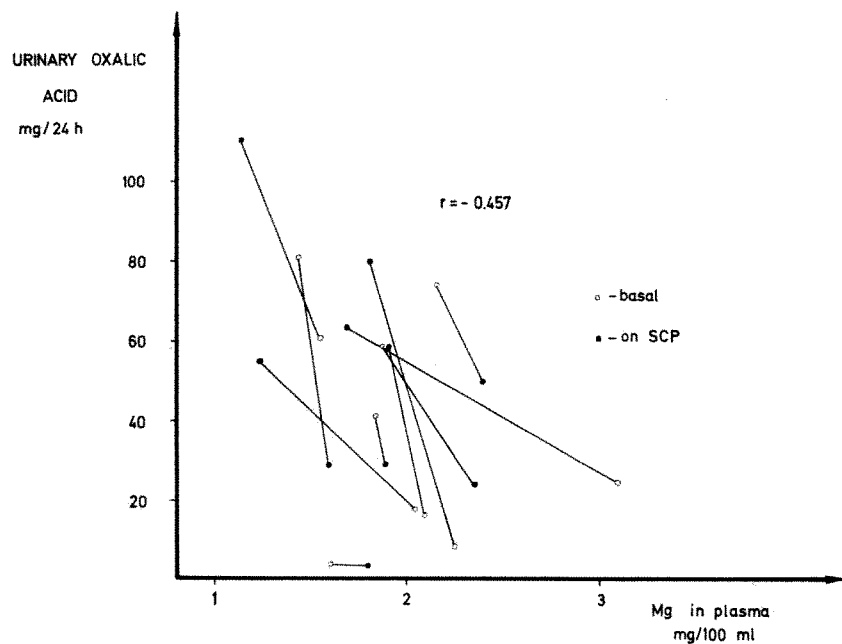


Fig. 4. The plot of urinary oxalate excretion versus plasma magnesium concentration (linear correlation coefficient = 0.457)

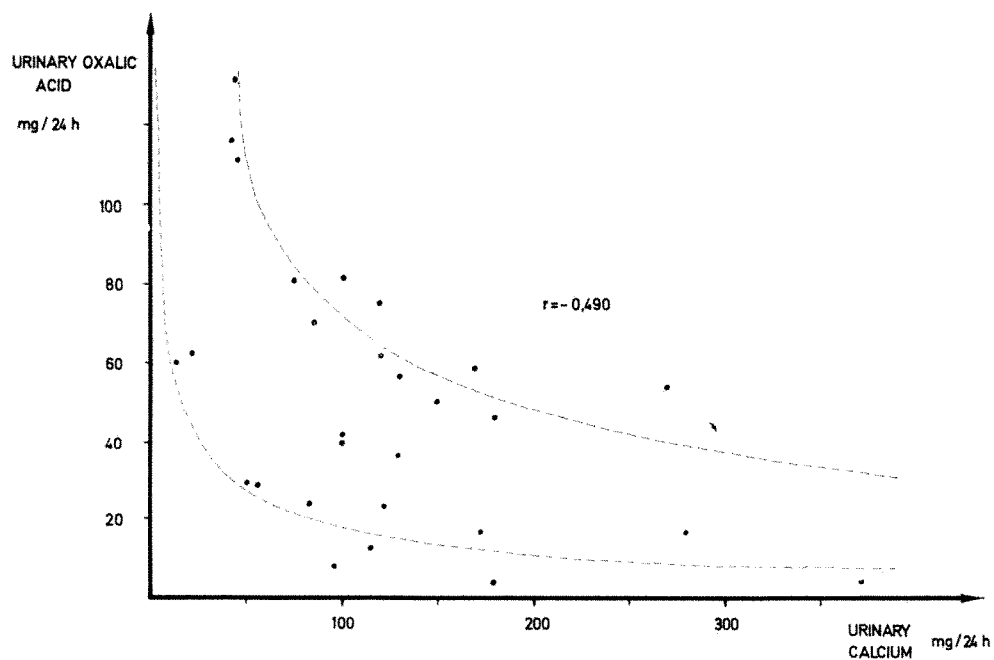


Fig. 5. The relation between urinary oxalic acid and urinary calcium excretion. The correlation coefficient and regression equations were calculated for decimal logarithms of both parameters. The graph only suggests but does not prove the hyperbolic relation.

periodic magnesium supplements and/or adjusting the dose of SCP to dietary calcium content in the individual patient.

Conclusion

Long-term follow-up of 11 patients seems to justify the opinion that cellulose phosphate is the drug of choice in the control of hypercalciuria and can be useful in the prophylaxis of the formation of calcium-containing kidney stones. This substance may contribute to the prevention of recurrent nephrolithiasis occurring in more than 30 per cent of urologic patients operated on for renal stones (J. Zieliński—personal communication), (Kollwitz *et al.*, 1969). The only significant side-effect of prolonged treatment is hypomagnesaemia which requires periodic monitoring and magnesium supplementation.

Summary

Sodium cellulose phosphate (SCP) was administered in a dose of 15 g per day to 2 patients with hyperoxaluria and to 11 stone-formers (8 with and 3 without hypercalciuria).

Urinary calcium excretion decreased in all patients up to 50 per cent or less of basal values. Attacks of renal colic and the passage of small stones became less frequent.

In the course of treatment a trend towards lower, although statistically not significantly lower, levels of serum magnesium, iron, copper and zinc concentrations was observed.

In 2 patients with primary hyperparathyroidism symptomatic improvement of hypercalcaemia was observed.

No subjective side-effects were noted; renal and liver function tests, blood cells and serum electrolytes did not show any change in the course of prolonged treatment with SCP.

Four out of 10 patients exhibited lower levels of oxaluria after treatment. An increase of oxaluria was found mainly in those patients in whom a fall of magnesium levels developed in the course of treatment.

We would like to thank Mr R. Bottomley from Whatman Biochemicals Ltd., Maidstone, Kent, England who amply contributed to this study by a generous supply of sodium cellulose phosphate in 5 g sachets; as also Messrs T. Choraży, Pharm.D., and A. Mielnikow, B.Sc., from the Central Mining Institute, Katowice, Poland who kindly performed the micro-elements determinations by means of atomic absorption (atomic absorption spectrophotometer type Unicam SP-90).

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Retrocaval Ureter

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Retrocaval ureter is a congenital venous anomaly where the ureter passes behind and is compressed by the inferior vena cava.

The latter may be apparently normal in calibre and position, be partially duplicated with both limbs on the right side and the ureter between them, or each limb lying on either side of the aorta and one or both ureters being retrocaval (Young, 1947).

Hochstetter in 1893 described the first case seen on autopsy, and Kimborough in 1935 did the first successful correction in a case diagnosed during surgery. The first pre-operative diagnosis was made by Harril (1940) who described the 29th case.

Retrocaval ureter may co-exist with a solitary kidney (Younger, 1960) or anomalies of the contralateral kidney such as hypoplasia (Murphy, 1963) and ectopia (Goyanna *et al.*, 1946). Spontaneous rupture of the hydronephrotic kidney was described in a woman (Oshin, 1964) 3 days after a normal delivery, and in 1 of our cases it was due to lumbar trauma (case 3, Table). The ureter may indeed be kinked by a lumbar or a gonadal vein as was described by Dreyfuss (1962) in a case of hydronephrosis in which the ureter was surrounded by a short aberrant vein coming from the psoas and draining into the posterior aspect of the vena cava.

Symptoms and Causes of Obstruction

In 80 per cent of the cases some or all of the symptoms are due to the obstruction. Continuous or intermittent lumbar pain, ranging from mild distress to renal colic, is present in two-thirds of the cases, associated or not with infection or albuminuria.

Calculi are found in 10 per cent of the cases and may be responsible for haematuria (Bitker, 1966).

Varying degrees of obstruction and the wide range of symptoms may account for the rarity of diagnosis in children and the discovery of the unsuspected anomaly at autopsy or during surgery. The condition is more frequent in men than in women (2.8 : 1) and is generally found in the fourth decade (Considine, 1966).

Renal ptosis is incriminated by some authors as an exacerbating cause for the obstruction and nephropexy is advised after correction of the primary condition. This holds as long as the ureter is behind the vena cava, but once it is re-anastomosed in front of it, a nephropexy is hardly necessary. In none of our cases was it performed.

The fibrotic process enfolding both the ureter and the vena cava, has a variable intensity and sometimes one is forced to leave these structures *in situ* not trying to separate them (Greene and Kearns, 1946; Campos Freire, 1953; Younger *et al.*, 1960; Rocha Brito and De Magalhães, 1962). They seem to be surrounded by a true localised retroperitoneal fibrosis.

Diagnosis

Urography may show hydronephrosis without a definite cause or the characteristic image of a reversed J with the dilated ureter approaching usually the third lumbar vertebra. Cineradiography may show it more precisely as well as the degree of the obstruction.

Retrograde uretero-pyelography discloses the typical italic S image with the Randall and

Campbell (1935) sign or the permanent proximity of the ureter to one or more vertebral bodies. This sign will not be found if a double right vena cava is present (Pick and Anson, 1940). More details can be found in the papers of Sesboué (1952) and Mullen and Engel (1952).

When the ureteral catheter is placed in the retrocaval segment one feels a certain resistance when trying to reach the renal pelvis.

The cavagram with ureteral catheterisation or uretero-pyelography, and even a simple catheter inside the vena cava (Goodwin *et al.*, 1957) are methods used in order to confirm a doubtful case.

Radio-isotopes are mainly worth while in the postoperative follow-up. The Hippuran Renogram with ^{131}I may indicate improvement of the ureteral drainage. ^{203}Hg scanning during the pre- and post-operative period may give an idea of the functioning parenchyma.

Case Reports

Case 1. D. N. P., aged 27, Register 7.640, had been treated previously for pulmonary tuberculosis, and was examined in 1955 on account of right renal colic for the past 3 days, normotension, haematuria and pyuria. Physical examination was normal. Urography and uretero-pyelography showed mild hydronephrosis caused by a calculous retrocaval ureter. At operation, the right kidney was exposed through an intercostal approach and the dilated ureter severed at its caudal end in order to liberate and uncross the ureter and vena cava. Uretero-lithotomy was performed above the section and a T-ureterostomy tube left in place. The retrocaval segment was excised because of fibrosis, the ureteral ends spatulated and a vertical incision made in order to enlarge the anastomotic diameter. The everting sutures were of atraumatic chromic 40 catgut. After an uneventful convalescence the patient was discharged on the 10th day and the tube removed on the 28th day after radiological control. Ten years later he passed an ureteral calculus from the left side, the right side was normal.

Case 2. A. C., aged 64, Register 10.798, was first seen in December 1957 having had right renal colic 1 year and 1 week before this examination. Haematuria and dysuria were present together with mild prostatism and hypertension. On examination an enlarged and painful right kidney was found as well as a grade 2 prostatic hypertrophy without any residual urine. Urography showed a normal left kidney but no opacification on the right side and 6 renal and 1 ureteral calculi. Retrograde uretero-pyelography demonstrated deviation of the ureter with calculus hydropyonephrosis (Fig. 1). Exploration disclosed marked perinephritis and the retrocaval ureter was so adherent to the vena cava that it was left *in situ* and a nephrectomy done. The specimen showed an evident ureteral stenosis (Fig. 2). A 1-year follow-up showed a normal left kidney.

Case 3. H. V., aged 14, Register 11.634, had suffered a lumbar injury without haematuria 15 days before, in June 1961. He had been treated in another hospital but the lumbar palpable mass had enlarged in the 2 days before examination. It was cystic on palpation and extended as far as the right iliac fossa. Urography showed a normal left kidney and a huge right kidney with only the superior calyces excreting and upwardly dislocated (Fig. 3). After right renal uretero-pyelography and catheterisation, it was misdiagnosed as a rupture in a double right hydronephrotic kidney (Fig. 4). The ureteral deviation toward the spine was attributed to the huge mass. Exploration disclosed a 1,000 c.c. right hydronephrotic kidney associated with a retrocaval ureter showing intense fibrotic adhesion to the vena cava. Right nephrectomy was done leaving the retrocaval segment *in situ*. The patient was seen 3 years later and was well.

Case 4. E. T., aged 53, Register 16.304, was seen in May 1968 complaining of intermittent right lumbar pain for the past 2 years. On examination the right kidney was palpable and painful. Urography showed a normal left kidney and a right hydronephrosis with the reversed J image of the ureter. Retrograde uretero-pyelography confirmed the retrocaval ureter and at exploration this was easily dissected and separated from the vena cava. The operative steps were similar to those in case 1, except that there was no calculus and the drainage was done by a nephrostomy and a size 8F splint via the inferior calyces. The latter was removed on the 6th day, after radiological control. The patient was discharged on the 8th day but readmitted on the 15th postoperative day with pulmonary embolism which soon resolved. Following this the nephrostomy tube was removed and leakage occurred for 2 days and then stopped spontaneously. Two years later the patient was free of symptoms and the right kidney was normal on the urography.

Case 5. N. V. C., aged 22, Register 22.599, was seen in April 1969 complaining of lumbar pain for 4 years and urinary infection. He had been treated for the last 6 months as a case of nephrosis in another hospital because of oedema and albuminuria. On examination he showed no oedema, the blood pressure was 120/80 mm Hg and a primary luetic lesion was found; 3,900,000 red cells, 12.0 g per cent haemoglobin, 35 per cent haematocrit and 7,600 white cells,



Fig. 1

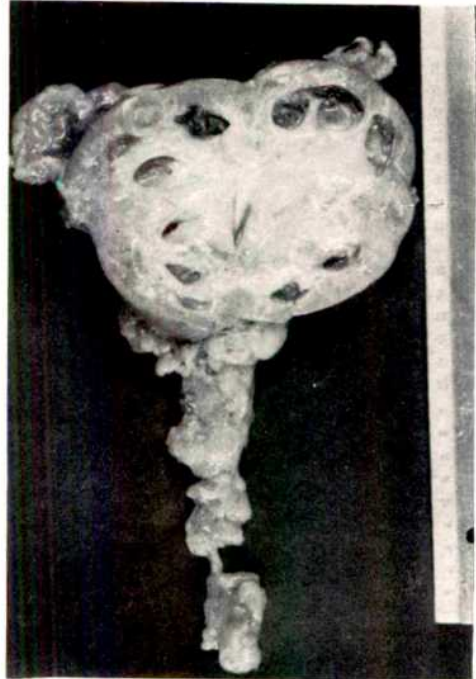


Fig. 2

Fig. 1. Case 2. Retrograde uretero-pyelography with RCU and calculous hydronephrosis.

Fig. 2. Case 2. Specimen with ureteral stenosis.

Fig. 3. Case 3. Urography showing huge mass and excreting superior calyces at right. A double kidney with rupture in the hydronephrotic inferior segment was suspected.

Fig. 4. Case 3. Retrograde uretero-pyelography showing the RCU course, and renal trauma.

RCU = Retrocaval ureter.



Fig. 3

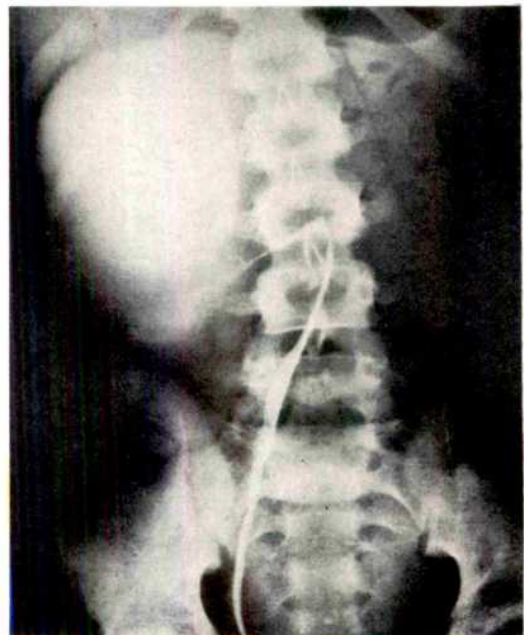


Fig. 4

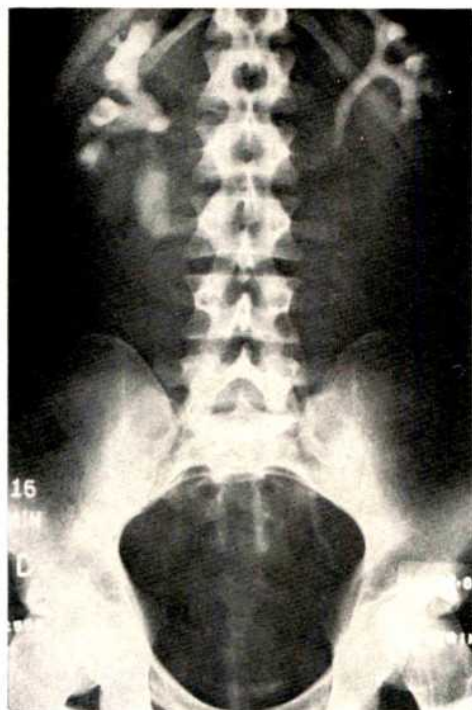


Fig. 5



Fig. 6

Fig. 5. Case 5. Urography showing typical reversed J image of the RCU at right.

Fig. 6. Case 5. Retrograde uretero-pyelography showing italic S aspect of the RCU. Associated cavagram.

Fig. 7. Case 5. Postoperative infusion urography.
RCU = Retrocaval ureter.



Fig. 7

80 mg per cent blood urea. Urography showed a normal left kidney and a right hydronephrosis with the typical reversed image (Fig. 5). Retrograde uretero-pyelography (Fig. 6) associated with a cavagram confirmed the retrocaval ureter. Through an intercostal incision the structures were easily dissected; the inferior pole of the kidney showed mild scarring from pyelonephritis. Renal biopsy revealed mild degenerative tubular alterations with some hyaline casts within them, but it was not adequate for glomerular study. The operative procedure was similar to that in cases 1 and 4 and an intubated nephrostomy was performed for drainage. Convalescence was complicated by an exacerbation of the infection, 1,000 ml of blood were necessary, and the patient discharged still on drainage on the 10th postoperative day. He was readmitted on the 30th day with a new exacerbation of the infection which was controlled by 120 mg/day of Gentamicin. Following this the nephrostomy tube was removed on the 33rd day, after radiological control and no leakage was noted. Nine months later and without any further medication urography showed a good postoperative result (Fig. 7).



Fig. 8

Fig. 8. Case 6. Urography showing dilatation of the double pelvis and a ureteral calculus

Fig. 9. Case 6. Retrograde uretero-pyelography with the RCU image.

RCU = Retrocaval ureter.



Fig. 9

Case 6. J. J. M. C., aged 29, Register 23.327, was seen in April 1970 with a history of right renal colic 4 years previously followed during the last year by lumbar discomfort and symptoms of infection. On examination the blood pressure was 120/80 mm Hg and the right kidney painful. Urography revealed a normal left kidney but the right kidney showed a double pelvis and mild hydronephrosis associated with a ureteral calculus near the third lumbar vertebra (Fig. 8). It was felt that the degree of dilatation did not correlate well with the size of the calculus and retrograde uretero-pyelography showed the true cause (Fig. 9). A cavagram confirmed the retrocaval ureter and a normal vena cava. A renogram ^{131}I (Fig. 10) showed delayed take-up and excretion by the right kidney. ^{203}Hg scanning gave an idea of the available renal parenchyma. The operative steps were similar to those in cases 1, 4 and 5 except that much more of the supracaval ureter was resected and a formal uretero-pyelo-anastomosis was performed. The resected ureter showed muscular hypertrophy and inflammatory changes. As there was no infection, no drainage was necessary. Convalescence was uneventful without any leakage and a postoperative renogram (Fig. 11) showed almost normal ureteral drainage. The patient was seen free of symptoms 6 months later.

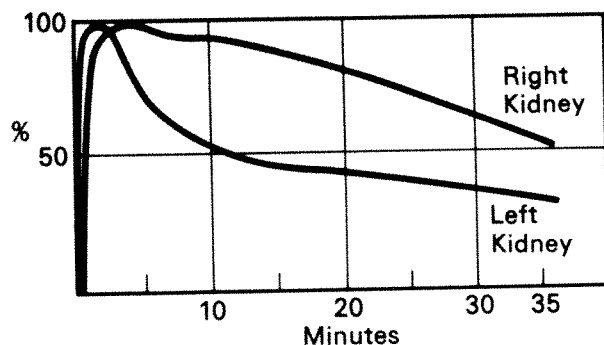


Fig. 10. Case 6. Pre-operative ¹³¹I renogram showing delay in the incorporation-excretion phases by the right kidney.

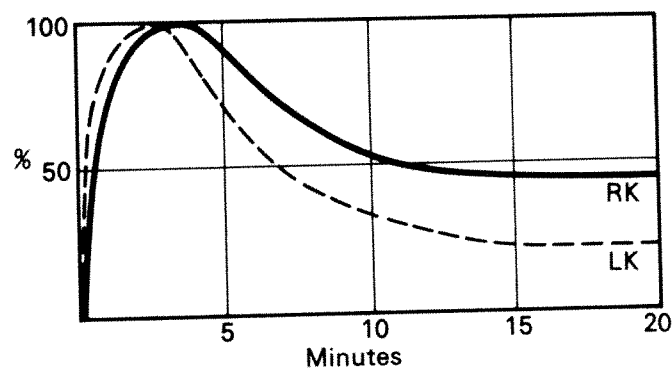


Fig. 11. Case 6. The 9th postoperative day ¹³¹I renogram showing an almost normal curve by the right kidney.

Comment

The pre-operative diagnosis of retrocaval ureter is important in planning the surgical correction for each case. This rare but well-known entity should be remembered when dealing with hydronephrosis. Our 2 cases involving nephrectomy were those diagnosed at operation but the degree of renal destruction in each would not have permitted conservative surgery. Case 2 was thought to be a calculus hydronephrosis and case 3 diagnosed as a large hydronephrosis in a double kidney with injury by trauma.

The reversed J image on urography elucidated 2 cases (Table) but dilatation without an explicit cause or in disproportion to any calculus present was more common (Figs. 3, 5, 8 and Table).

The most precise examination to confirm the presence of retrocaval ureter was retrograde uretero-pyelography (Figs. 1, 4, 6, 9 and Table).

A cavagram associated with retrograde uretero-pyelography may be very helpful in confirming a doubtful case. It is easily performed by injecting 40 to 60 c.c. of Hypaque 75 per cent quickly into the right femoral vein.

TABLE

Case	Register	Year	Sex	Age	Renal Colic	Haematuria	Infection	Proteinuria	Lithiasis	UROGRAM			Uretero- pyelogram	Cavagram	Isotopes	Pre-op Diagnosis	Technique of Anastomosis	Partial Ureterectomy	RC Ureter <i>Left in situ</i>	DRAIN- AGE		Urinary Leakage	Complications	Follow-up (Years)	Results
1	7.640	1955	M	27	+	+	+	+	+	Dilatation	Exclusion	Inverted J	+	+	+	U	+	+		TU	28			10	G
2	10.798	1957	M	64	+	+			+	4+			+	+		N	N		+					1	G
3	11.634	1961	M	14	RT					4+	+		+	+		N	N		+					3	G
4	16.304	1968	M	53	+					+		+	+	+	+	U	U	+		NS	16	2 days	PE	2	G
5	22.599	1969	M	22	+		+	+		+		+	+	+		U	U	+		IN	33		I	1	G
6	23.327	1970	M	29	+	+	+		+	+			+	+	+	UP	UP	+		NO				1/2	

U = Uretero-uretero anastomosis.
 UP = Uretero-pyelo-anastomosis
 N = Nephrectomy.
 RT = Renal trauma.
 TU = T ureterostomy.

NS = Nephrostomy + splint.
 IN = Intubated nephrostomy.
 NO = No drainage.
 PE = Pulmonary embolism.
 I = Infection.
 G = Good.

The usefulness of radio-isotopes is mainly in measuring the postoperative results. The pre- and postoperative ^{131}I renograms in case 6 (Figs. 10 and 11) show the obstructed as well as the free ureteral drainage. An idea of the available renal parenchyma is afforded by means of ^{203}Hg scanning.

Haematuria is indicative of a complicating lithiasis. It was present in 50 per cent of our cases although the average incidence seems to be around 10 per cent (Bitker, 1966). Albuminuria may also be present as for instance in case 5, where associated oedema led to the patient being treated for the nephrotic syndrome elsewhere. A renal biopsy in this case showed mild degenerative tubular alterations with some hyaline casts within them, but it was not sufficient for a glomerular study. After surgical correction, however, the albuminuria fell promptly without further treatment.

A mild systolic hypertension was found in cases 2 and 4, but it was attributed to the patients' age and not to the kidney.

Summary

The authors present 6 cases of retrocaval ureter treated by conservative surgery (4 cases) and nephrectomy (2 cases). One case simulated the nephrotic syndrome and 1 patient had a kidney rupture caused by lumbar trauma.

Attention is focused on pre-operative diagnostic methods, radio-isotope investigation and certain aspects of surgical technique involved in the treatment of the condition.

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Postmenopausal Endometriosis with Ureteral Obstruction

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Endometriosis characterised as "a benign neoplastic metastasizing disease" (Stanley, 1971) is the condition wherein normal endometrium exists in an ectopic location (Berlin, 1964).

Since its first description at autopsy by Rokitansky in 1860, the incidence has gradually increased to where 10-20 per cent of women are affected by it during the child-bearing age. Most cases occur between ages 25 and 40 with peak incidence from 30 to 35. It has been previously reported as early as 18 and as late as 50 (Abeshouse, 1960).

In 1938 Meigs suggested the disease was socio-economically related since it is more common among the better educated and more affluent. It is more likely, though, that this relationship is due to later and fewer pregnancies. Certainly this would fit with the migratory theory of endometrial metastasis since the nulliparous os might be expected to pass menstrual products less readily with transtubal intraperitoneal spill resulting (Sampson, 1921).

Recently an unusual case of endometriosis involving the urinary tract presented to us with the onset after the menopause. Postmenopausal endometriosis is an uncommon but well-known entity to gynaecologists but its existence may not be widely known to urologists. This case is, to our knowledge, the first patient with postmenopausal endometriosis involving the urinary tract.

Case Report

J. M., a 56-year-old nulliparous white woman presented in December 1968 with cramping abdominal pain in the left lower quadrant and left back pain of 3 month's duration.

It was noted that she had been on conjugated oestrogen ("Premarin") therapy 1.25 mg daily since a pan-hysterectomy, 11 years previously.

On examination a tender mass was noted in the left lower quadrant of the abdomen and in the rectovaginal pouch. Mild left costovertebral angle tenderness was noted.

Laboratory and X-ray investigation included: urinalysis—within normal limits; a barium enema showed compression and displacement posteriorly of the rectosigmoid without intrinsic disease (except for diverticulosis); and intravenous pyelography which showed dilation of the left collecting system and ureter to just below the pelvic brim. (Fig. 1).

At exploration a hard, fixed mass with multiple chocolate-brown cysts was found between the urinary bladder and the rectosigmoid overlying the left ureter. The presumptive diagnosis of endometriosis made on gross examination of the mass was confirmed by rapid frozen section biopsy. The abdomen was closed.

During the uneventful postoperative course, the conjugated oestrogens were discontinued.

A follow-up excretory urogram 7 months later revealed considerable resolution of the previously seen dilatation (Fig. 2). Two and a half years later the urogram was normal (Fig. 3).

Review of the panhysterectomy specimen 11 years previously showed no histological evidence of endometriosis in the uterus, fallopian tubes, ovaries or pelvic peritoneum of the pouch of Douglas.

Comment

Since retrospective examination of the total hysterectomy specimen did not show endometriosis at the time of operation, the pathogenesis must have been by spillage of endometrial tissue from



Fig. 1. I.V.P. Dilation of left ureter to pelvic brim.



Fig. 2. I.V.P. Seven months later: reduced dilation.

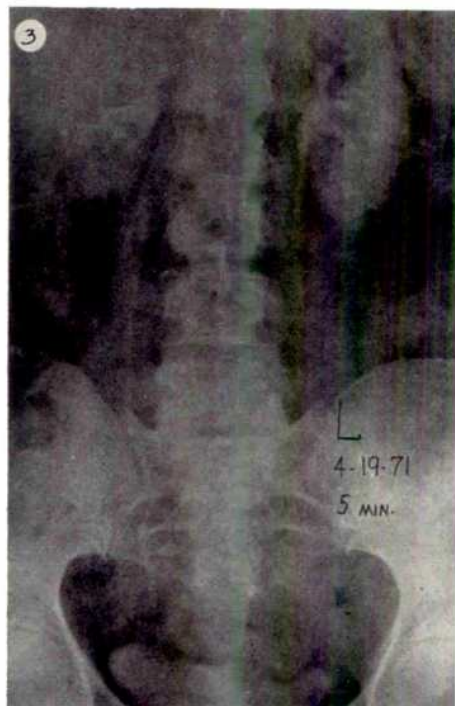


Fig. 3. I.V.P. Two and a half years later: normal.

the uterus while removing it or by metaplastic change of the peritoneal surfaces under the influence of the exogenous oestrogens. Of the two possibilities, certainly the former seems to us the more plausible.

Arrest of ovarian function, by whatever means, usually causes an abrupt cessation in activity of endometrial tissue but, occasionally, castration does not arrest it (O'Connor, 1945). Either the tendency to infiltrate has become independent of hormone control (Kempers, 1960) or there is significant oestrogen from extra-ovarian (adrenal or pituitary) sources. Persistence of oestrogen has been reported even after both oophorectomy and adrenalectomy, and is postulated to be due to aberrant adrenal cortical tissue or pituitary origin as is seen in cattle and horses (Struthers, 1956). In our case the source was, of course, exogenous.

Summary

The first case of postmenopausal endometriosis involving the urinary tract is reported. Incidentally this is the 65th reported case of ureteral obstruction from endometriosis.

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The Effect of Testosterone on the Human Prostate in Organ Culture

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Current attempts to influence benign prostatic hypertrophy by hormone therapy are based on the assumption that the growth of the prostate in benign hypertrophy is under the influence of testosterone and related androgens. It has not, however, been shown that alteration in the hormone environment by surgical castration brings about any change in the clinical course of benign hypertrophy (Moore, 1944) and reported trials with hormone therapy "do not show clinical improvement that is more than marginal" (Editorial, *British Medical Journal*, 1971).

Experimental evidence is conflicting. Although specific uptake of testosterone by the human prostate (Ghanadian *et al.*, 1972) and stimulation of prostatic DNA—polymerase by testosterone (Harper *et al.*, 1969) have been shown to occur, it has not yet been demonstrated that either the metabolism or the structure of benign hypertrophy is altered by testosterone deprivation. The prostate in animals appears to be testosterone dependent, but does not undergo comparable benign hypertrophy. Lasnitzki (1965) has shown that in the absence of testosterone, the epithelium of the rat ventral prostate in organ culture becomes flattened, the acini unfolded and the stroma more cellular. These changes can be prevented or reversed by the addition of testosterone to the culture medium, but it may be important that they are more marked in organs from immature animals.

Attempts at reproducing these changes in the human prostate have so far been largely unsuccessful. Wojewski and Przeworska-Kaniewicz (1965) could find no changes in epithelial outgrowths in the absence of testosterone in tissue culture; Röhl (1959) claimed some androsterone-stimulated growth in 1 out of 4 human prostate specimens; Franks (1970) and McMahon (1970), in large numbers of experiments, have been unable to demonstrate any morphological hormone dependence.

This apparent failure of testosterone to influence benign hypertrophy in organ culture may be due to one of three reasons. Firstly, the tissues in organ culture may not behave as they do *in vivo*. Although it has not been established in all aspects, it has been shown that in organ culture the hypertrophied prostate takes up and metabolises testosterone in a similar way, both qualitatively and quantitatively (McMahon and Thomas, 1970), to incubation experiments (Ghanadian *et al.*, 1972) and to *in vivo* experiments in animals and man (Pike *et al.*, 1970). Secondly, benign prostatic hypertrophy may not be hormone dependent at all. Thirdly, the length of time that cultures have been maintained may be insufficient to demonstrate morphological changes. It may be that biochemical measurements are needed to demonstrate dependence over these relatively short periods. Examination of aspects that are known to be androgen dependent in animals, such as DNA and acid phosphatase production, should indicate whether or not human prostatic metabolism is androgen dependent in organ culture.

Materials and Methods

Specimens were taken from 29 prostatic adenomata at open prostatectomy. A section from the centre of the adenoma was selected, washed briefly in a balanced salt solution and transported

at 4°C. Cultures were established within 45 minutes of operation. Under sterile conditions the specimen was divided into 2 × 3 mm explants which were placed on dry cover slips in Leighton tubes, 3 explants to a tube. Six to eight tubes were set up for each prostatic adenoma. The tubes were weighed before and after adding explants and the weight of the tissue calculated. The total weight of tissue varied between 10 and 20 mg per tube. One ml of culture medium consisting of Eagles Minimum Essential Medium with 10 per cent calf serum, insulin 13.8 µg/ml and penicillin 3 µg/ml was added to each tube. The tubes were gassed with 95 per cent O₂ and 5 per cent CO₂ and placed on a rotating frame in an incubator to rotate at 12 revs/hour.

Cultures were incubated at 37°C for 4 days after which the medium was changed and the tubes divided randomly into 2 groups. Thus, half of the culture tubes served as controls; to the other half, testosterone was added to give a final concentration of 3.5×10^{-5} M. After incubation for a further 4 days, the medium was removed and explants estimated for DNA and tissue acid phosphatase content. Specimens from each adenoma were examined histologically and glucose determinations were carried out using the glucose oxidase method (Sunderman and Sunderman, 1961) with an autoanalyser; the error of the method was 10 per cent. DNA was estimated colorimetrically after extraction with perchloric acid, and acid phosphatase was determined after incubation with phenolphthalein diphosphate (Ghanadian *et al.*, 1972). The error of these methods was less than 10 per cent.

Results

29 prostatic adenomata were examined in organ culture. Four experiments were discarded because of either non-viability of the whole culture or infection. Although several specimens showed histological evidence of infection, organisms seemed rarely to establish themselves in the presence of the antibiotics.

Histology

Histological examination showed considerable epithelial loss during the first 4 days, the cells being shed into the lumina of the acini and remaining there as cell debris throughout most of the culture period. After the fourth day, there was marked epithelial proliferation from the basal layers of the acini and at the end of the 8 days of the experiment the cells were active and dividing with numbers of mitotic figures. The general acinar pattern was usually well maintained, but at times areas of solid proliferation and creeping of epithelium around the edges of the explants occurred. On some occasions considerable epithelial outgrowths extended from the explants on to the cover-slips. The stroma was less well maintained, but usually remained in all elements and excessive fibroblastic proliferation was not seen. There was comparable maintenance of structure and, overall, there were no morphological differences between those cultured with and those without testosterone (Fig. 1, A, B).

Glucose Utilisation

Glucose utilisation was fairly constant within cultures from each prostate, but varied between different prostates (Table). During both periods of 4 days, the rate of utilisation varied between 0.02 and 0.17 µmole/g of tissue per 24 hours. During the second period there was no difference in glucose utilisation between those explants cultured with, and those without, testosterone.

In 9 prostates, there was an increase in the rate of glucose utilisation during the second period compared with the first; 4 showed a decreased rate and in 2 there was no change. Again there was a constancy in response within cultures from the same prostate, and no difference in the amount or direction of the change between those cultured with and those without testosterone.

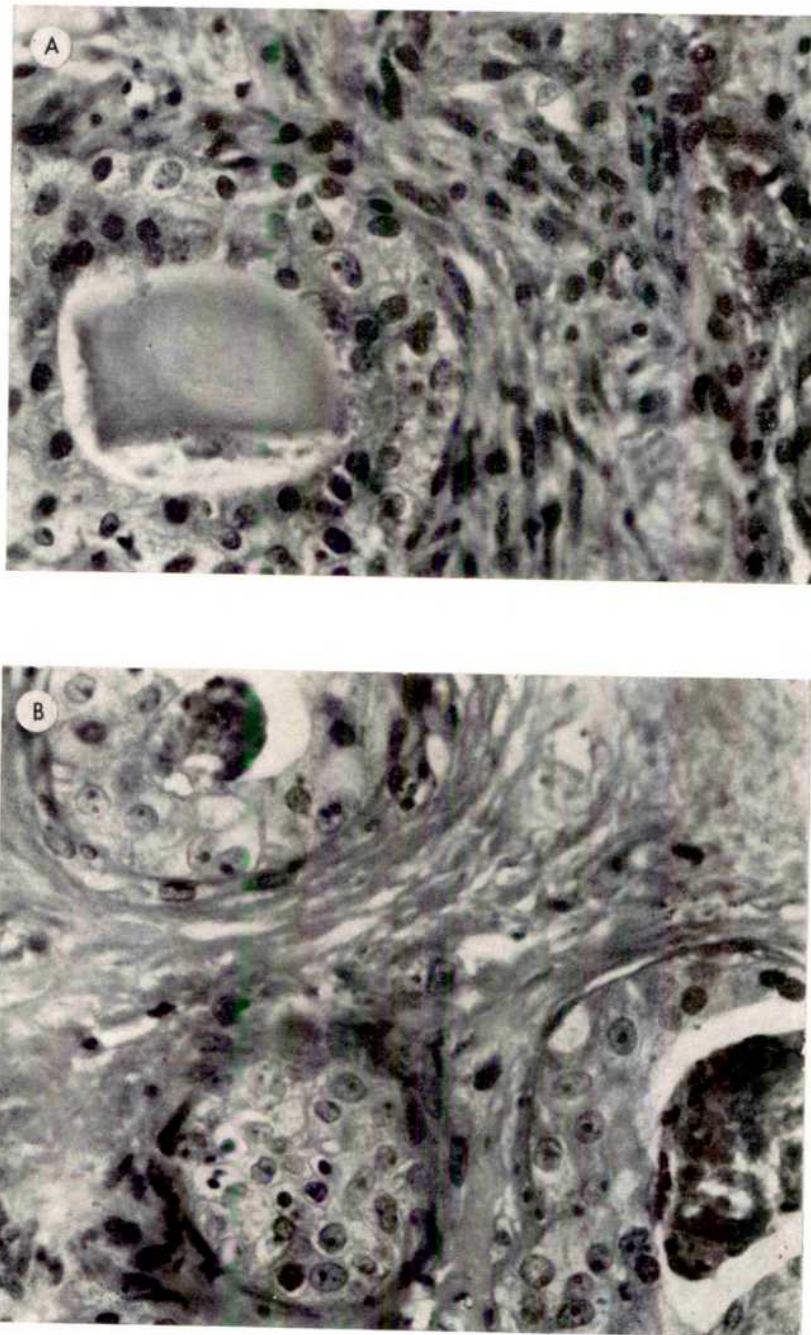


Fig. 1. Explants after 8 days culture. A, Control. B, Testosterone 3.5×10^{-5} M. (H & E $\times 400$).

Table

Glucose Utilisation during the Two Periods of Study—
Days 1-4 and Days 5-8—expressed as $\mu\text{moles/g/24 hr}$
($\pm$ standard deviation)

Prostate No.	Days 1-4	Days 5-8	
		Control	Testosterone $3.5 \times 10^{-5}\text{M}$
5	0.04 ± 0.007	0.06 ± 0.016	0.06 ± 0.008
6	0.17 ± 0.048	0.1 ± 0.039	0.13 ± 0.013
7	0.06 ± 0.013	0.04 ± 0.009	0.04 ± 0.006
9	0.05 ± 0.013	0.05 ± 0.01	0.06 ± 0.015
10	0.04 ± 0.018	0.05 ± 0.005	0.04 ± 0.006
11	0.05 ± 0.009	0.06 ± 0.011	0.05 ± 0.005
12	0.06 ± 0.019	0.11 ± 0.038	0.09 ± 0.02
13	0.07 ± 0.012	0.1 ± 0.02	0.1 ± 0.005
15	0.08 ± 0.03	0.08 ± 0.02	0.1 ± 0.006
16	0.03 ± 0.02	0.02 ± 0.02	0.02 ± 0.01
17	0.1 ± 0.02	0.08 ± 0.02	0.07 ± 0.002
18	0.07 ± 0.01	0.11 ± 0.02	0.1 ± 0.01
20	0.05 ± 0.02	0.1 ± 0.04	0.08 ± 0.01
21	0.06 ± 0.017	0.06 ± 0.004	0.07 ± 0.02
22	0.04 ± 0.01	0.04 ± 0.01	0.06 ± 0.006

Acid Phosphatase

Tissue acid phosphatase concentration was estimated in 20 prostate experiments in which histological examination indicated comparable maintenance of structure. Three further experiments were not considered; because of marked difference in the viability of the 2 groups at the end of the culture period in 2, and a laboratory mishap in 2.

When tissue structure was well preserved, there was considerably more acid phosphatase in the testosterone treated explants than in the controls (Fig. 2). Considering the whole group, there was significantly more enzyme in explants grown in the presence of testosterone when each was compared with its control ($P=0.03$).

DNA

The concentration of DNA was measured in 21 experiments in which histological examination showed comparable maintenance of structure. DNA concentration was more uniform between cultures than was acid phosphatase (Fig. 3). All cultures contained significant amounts of DNA at the end of the culture period; in many the differences were small, but overall the cultures grown in the presence of testosterone contained significantly more DNA than did the controls ($P=0.03$).

Discussion

Once established, this technique for culturing the human prostate produces consistently good results as it does with other tissues (Morgan *et al.*, 1950; Barker and Richmond, 1971). In preliminary experiments, it was found that much inferior results were obtained when human cultures were maintained in Petri dishes on either filter paper or agar gel supports as used by others (Lasnitzki, 1965). Minimum Essential Medium appeared to produce better results than TC 199 when used as the basis of the culture medium, and this is consistent with the results of R  ller *et al.* (1966).

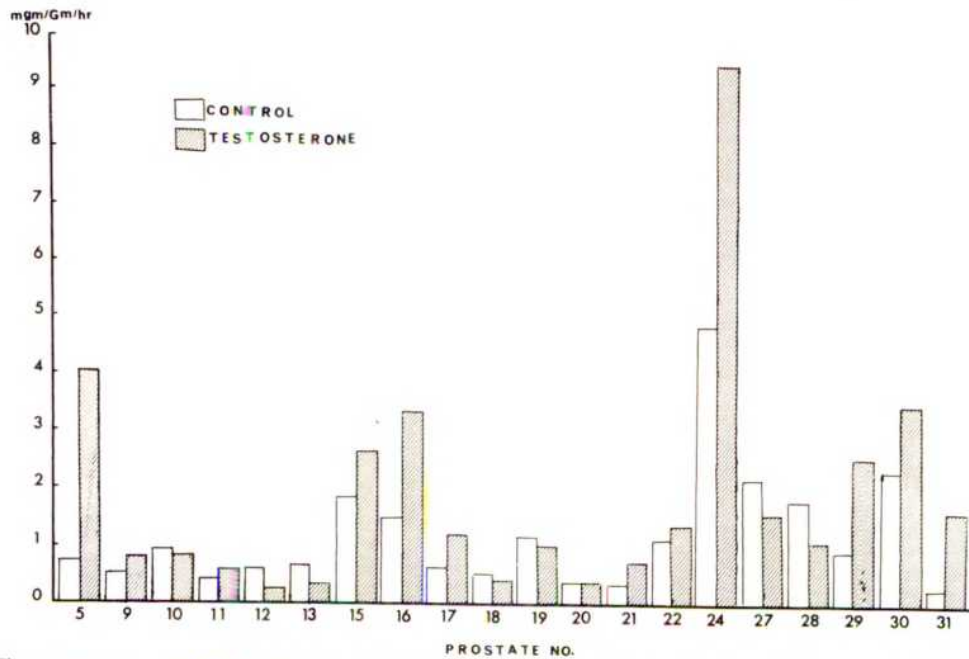


Fig. 2. Tissue concentrations of acid phosphatase after 8 days culture in 20 experiments. Concentrations in mg of phenolphthalein liberated per gram of tissue, per hour of incubation.

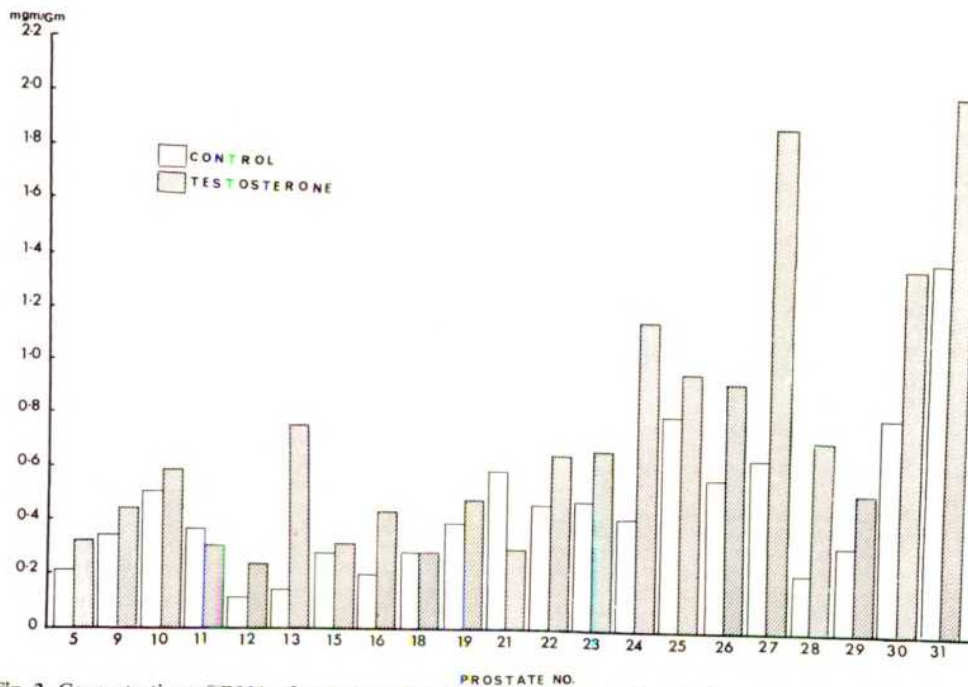


Fig. 3. Concentration of DNA after 8 days culture in 21 experiments. Results in mg DNA per gram of tissue.

The experimental period was limited to 8 days since it was found that after this time histological preservation became less consistent. Although cultures could at times be maintained with acceptable histological preservation for 3 weeks or longer, it was felt that acceptance of a shorter culture period would minimise the decrease in differentiation that could be expected to occur.

Glucose utilisation, DNA and acid phosphatase were chosen as representatives of oxidative and biosynthetic metabolism that could be accurately measured in the small amounts of tissue involved. It is known that in the animal prostate testosterone influences protein metabolism and enzyme systems such as acid phosphatase, but not oxidative metabolism (Farnsworth and Brown, 1961). Our results are consistent with this, indicating an effect on DNA and acid phosphatase, but no effect on glucose utilisation. Although the effects on DNA and acid phosphatase were statistically significant, the differences in each study were often small and sometimes lacked consistency; further improvements in techniques should improve the consistency in each study.

Organ culture provided a unique opportunity to study the effect of specific alterations in cell environment and has already provided much of the knowledge of the metabolism of testosterone and the action of its metabolites (Baulieu *et al.*, 1969). Clinical trials of drugs for the treatment of prostatic diseases are expensive, time consuming and not always based on good evidence of efficacy. If organ culture of human prostates can be developed so that there is a consistent and predictable response to testosterone, it will provide a rational basis for hormone therapy in benign prostatic hypertrophy and will provide a useful laboratory model, both for studying the metabolism of, and evaluating substances for, treatment of this condition.

Summary

A reliable method of examining human prostates in organ culture is described.

Preliminary investigations suggest that testosterone influences DNA and acid phosphatase production even in the absence of morphological changes.

Further development of this laboratory model may result in a method for studying the influence of various drugs on prostatic disease.

We wish to acknowledge the considerable assistance of Mr C. Richmond and Miss M. Feesey in setting up the cultures and preparing the histological sections.

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A Method of *in vivo* Maintenance of Human Prostatic Tissue in Immunosuppressed Mice

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With recent advances in steroid chemistry several compounds have been suggested as suitable for the medical treatment of human benign prostatic hypertrophy (BPH) (Geller *et al.*, 1965; Scott and Wade 1969; Castro *et al.*, 1971). Simple laboratory methods for assessing the value of these drugs are needed so that lengthy and expensive clinical studies can be confined to those agents most likely to be useful. However, the laboratory investigation of the prostate is difficult because experimental models are unsatisfactory. In this paper a new method for maintaining human BPH tissue in immunosuppressed mice is described.

Methods

Male CBA mice were obtained from Animal Suppliers Ltd. and were immunosuppressed by thymectomy, lethal irradiation and syngeneic bone marrow reconstitution.

The mice were thymectomised at 4 weeks of age by the sternal approach (Miller, 1961). Two weeks later they were given 900 r whole body irradiation from a cobalt source. Within 24 hours they received an intravenous injection of 5×10^6 cells of syngeneic (CBA) bone marrow, obtained by irrigating donor femurs and tibias with Eagles Minimal Essential Medium (MEM). Three weeks to 3 months later xenografts of human BPH tissue were implanted beneath the kidney capsule or subcutaneously.

BPH tissues were obtained at the time of open prostatectomy, placed in cold Eagles MEM and immediately transported to the laboratory for processing. A clean, but not sterile, procedure was adopted and the prostatic tissues cut into small fragments 1-2 mm³ for implantation into the prepared mice. Representative pieces of prostatic tissue were taken for baseline histology.

The prostatic tissue was implanted beneath the kidney capsule and subcutaneously in the region of the snout. For all experiments 6 mice were anaesthetised with Nembutal (Veterinary Nembutal (Abbott) diluted 1 : 10 with normal saline and given at a dose of 0.1 ml/10 g body weight). The left kidney was exposed through a loin incision and it was delivered to the surface of the wound, fine scissors were used to open the kidney capsule and watchmakers' forceps to place a piece of prostatic tissue under the capsule. The body wall and skin were closed with a single suture.

In the same animals prostatic tissues were implanted under the skin of the snout. A small incision was made over the occiput and forceps bearing the prostatic tissue were then passed subcutaneously downwards so that the implanted tissue was left lying on the nasal bones and the wound closed with a single suture.

Consecutive recipient mice were killed 2, 4, 8 or more weeks after implantation. The left kidney and skin of the snout were removed and placed in 10 per cent formal saline fixative. 24 hours later blocks were trimmed to the size of the tissue implants and the specimens were processed for histological examination. Three paraffin sections, taken at different depths of the block, were stained with haematoxylin and eosin and viability assessed by overall histological appearances; only when the implanted specimens were very similar to baseline histology were they considered viable.

Results

Prostatic tissue was obtained from 6 different patients and 2 weeks after implantation viable human prostatic tissues were obtained in all 6 cases maintained in the mouse host. The detailed results of specimens implanted under the kidney capsule are shown in Table I where viability at different intervals after implantation is shown. Preservation of histological appearances was excellent and histological sections from 1 case are shown in Figures 1 and 2. Figures 1 and 1A show the histological appearances of a specimen of human BPH obtained at the time of operation and Figures 2 and 2A show the histological appearances of prostatic specimens obtained from the same patient after they have been maintained in an immunosuppressed mouse for 2 weeks.

In Table II a comparison of viability at the subcutaneous site and beneath the kidney capsule is made.

Table I

Viability of Human BPH Tissues at Various Intervals after Implantation beneath the Kidney Capsules of Immunosuppressed Mice

Case Number	Interval after Implantation			
	2 weeks	4 weeks	8 weeks	12 weeks
1	+	+	+	—
2	+	+	—	+
3	+	+	—	...
4	+	+	+	...
5	+	+	+	...
6	+	+	...	...
Total	6/6	6/6	3/5	...

+ Viable — Necrotic

Discussion

This method of maintaining human BPH tissues worked well and the viability rate up to 1 month, when all specimens were maintained alive, makes it suitable for use as a method for further investigation of human prostate tissues *in vivo*.

In most instances the implanted tissue did not increase in size very much: the majority of specimens were 3-4 mm at time of removal and those removed at 2 months did not appear much larger than those at 1 month. In many cases, viability could be assessed accurately by the macroscopical appearance of a gelatinous pink tissue. Histological assessment of viability was not difficult and it is most unlikely that tissue organisation would be maintained for 2 weeks (the earliest time at which specimens were studied) if they were not viable. In some cases supplementary evidence of viability was obtained by positive staining for acid phosphatase and by the passage of maintained BPH tissue into a secondary immunosuppressed host. The results of these investigations confirmed the assessment of viability determined by examination of haematoxylin and eosin stained sections.

The mechanism by which the xenogeneic tissues were accepted by the mouse is certainly due to generalised immunosuppression. Thymectomy, lethal irradiation and syngeneic bone marrow reconstitution causes depletion of the number of thymus processed lymphocytes (Davies *et al.*,

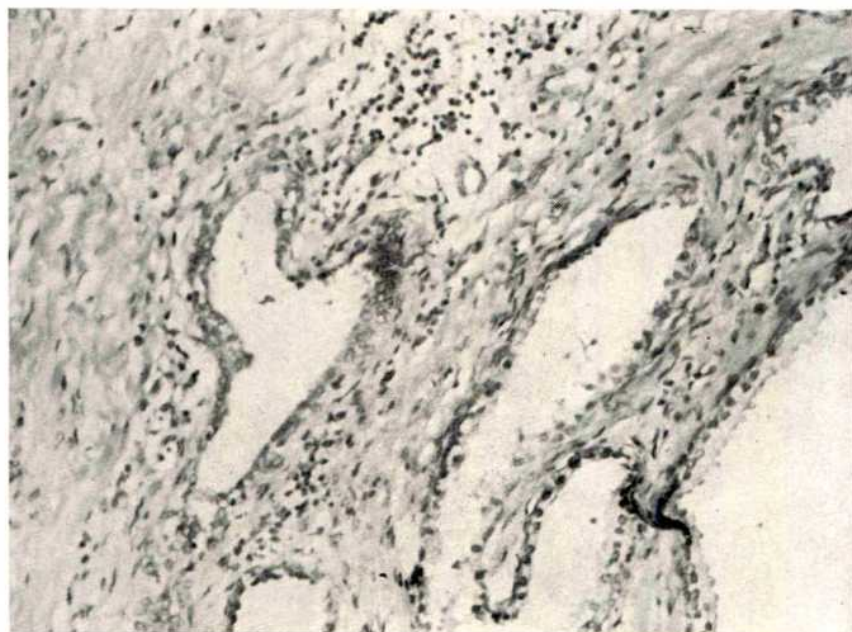


Fig. 1. Human BPH tissue: specimen obtained at the time of open prostatectomy (H & E $\times 50$).

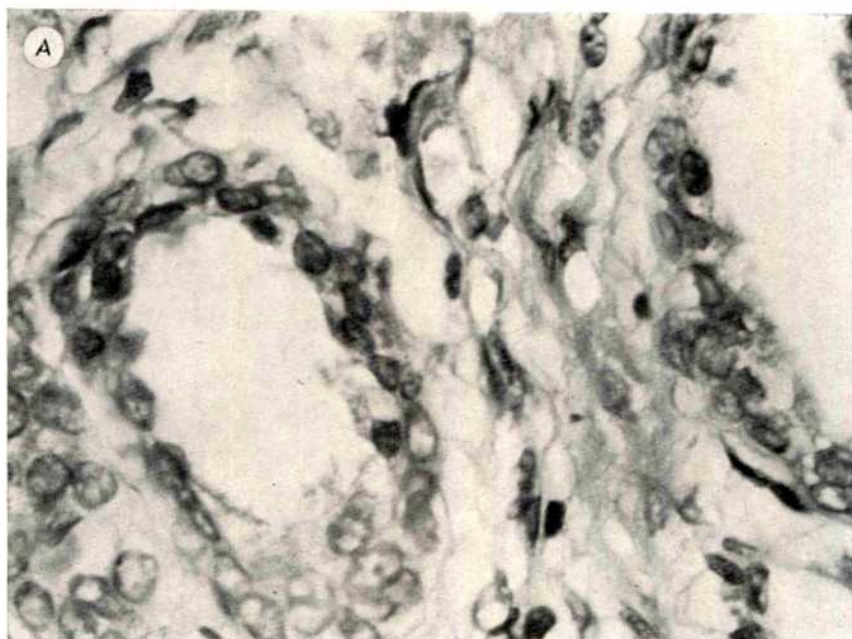


Fig. 1a. Human BPH tissue: high power view of specimen 1 (H & E $\times 200$).

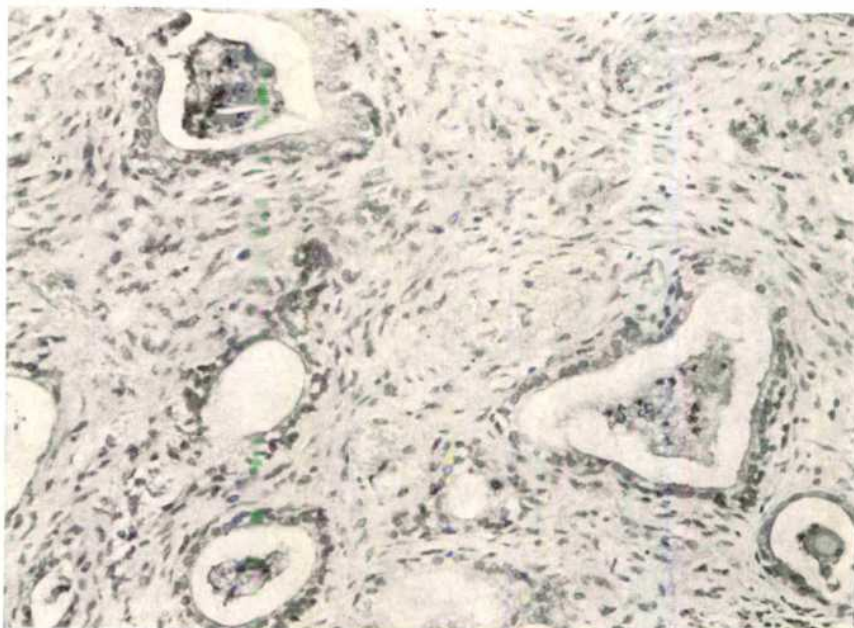


Fig. 2. Maintained human BPH tissue. A piece of prostatic tissue obtained from the same case as shown in Figure 1 but the specimen has been maintained in a thymectomised, irradiated bone marrow reconstituted mouse for 2 weeks (H & E $\times 50$).

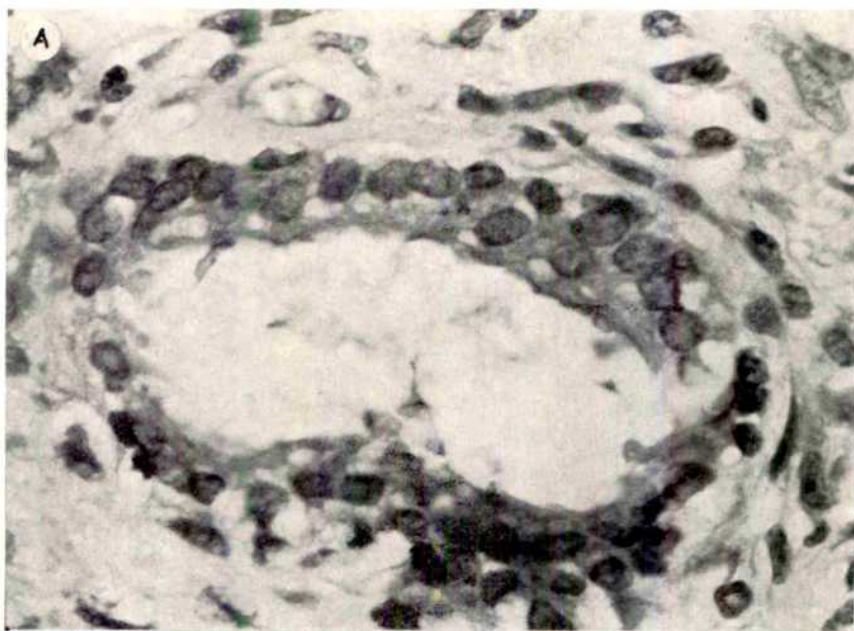


Fig. 2a. Maintained human BPH tissue. High power view of specimen 2 (H & E $\times 200$).

Table II

Comparison of Viability of BPH Tissues Implanted beneath the Kidney Capsule and Subcutaneously

Site	Kidney Capsule			Subcutaneous		
Time after implant	2 week	4 week	8 week	2 week	4 week	8 week
Total implanted	6	6	5	6	6	5
Total viable	6	6	3	6	4	3

1969) and decreases cell mediated immunity in these mice. However, such mice are still able to produce antibodies against the implant (Castro, unpublished observation) and it may be that this is the reason for a lower rate of viability after a longer period of implantation (Table I). Human prostatic tissues implanted into normal mice did not survive.

Tissue and organ culture methods have been used to maintain human BPH. However, in the intact animal prostatic growth is affected by a complex interaction of hormonal and systemic factors. When prostatic tissues are isolated and grown in culture these are eliminated, and whilst this may be advantageous in unravelling some basic physiological concepts, it might be a disadvantage in the assessment of possible therapies. It is probable that many agents will have an indirect effect upon prostatic growth, perhaps by altering the hormonal milieu such effects would be apparent in an *in vivo* situation.

Furthermore by using *in vivo* maintenance it is possible to assess the therapeutic/toxicity ratio of administered compounds. Finally, tissue culture may be associated with stromal proliferation while *in vivo* maintenance allows good histology to be obtained (Fig. 2).

Implantation beneath the kidney capsule was used as it produced a vascular site and slight pressure exerted by the capsule may aid vascularisation of the implanted specimen. However, it has the disadvantage that viability cannot be assessed by palpation. In contrast, implantation beneath the skin allows palpation of growing tissues but this advantage is mitigated by the slightly lower rate of survival (Table II) as compared to implantation under the kidney capsule.

Several other methods for *in vivo* study have been suggested but they too may have some disadvantages. BPH occurs naturally only in the dog, of the commonly used laboratory animals (Zuckerman and Groome, 1937); however, it differs from human BPH histologically (Mostofi, 1970) and physiologically (Goodpasture and Wislocki, 1916) producing rectal instead of urinary obstruction (Kracht-Paléjeff, 1911). The use of external prostatic fistulae in dogs (Scott and Schirmer, 1966) allows the influence of drugs on prostatic secretion to be studied but this is not necessarily an index of size and malfunction; furthermore, the problem of species differences has been alluded to. The induction of prostatic hypertrophy in other laboratory animals by administration of oestrogens has been described (Lacassagne, 1933; Fingerhut and Veenema, 1966), but the histological changes are not typical of human BPH (Moore and Price, 1932; Castro, unpublished).

Methods of growing human tissues in xenogeneic hosts overcome the problems of species differences. Many methods have been employed for growing human malignant (Toolan, 1951) or normal tissues (Chesterman, 1959) but in only one instance has the attempt been made to grow human BPH (Senge *et al.*, 1971). These methods employ the use of immature hosts which are naturally immunologically incompetent (Southam *et al.*, 1966), hosts which are specifically immunosuppressed by chemical and physical methods (Phillips and Gazet, 1968; Palm *et al.*, 1958) or the use of privileged sites. In all cases the viability ratio was low and, furthermore, the use of privileged sites may prevent therapeutic agents reaching the growing xenogeneic tissue.

The method described utilised human tissues, gave good viability and would allow assessment of agents acting indirectly by altering the growing environment of human prostatic tissues. A disadvantage is that because of immunosuppression this method would not permit study of alterations of host cell mediated immunity on the growing prostatic tissue.

Summary

A method for growing human prostatic tissue in immunosuppressed mice has been described. Many viable specimens were obtained from 2 weeks to 2 months after implantation. The implications of the method as a laboratory method for screening agents suitable for treating human BPH is discussed and the method is compared with other methods for the *in vitro* and *in vivo* study of human prostatic tissue.

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Prostatic Carcinoma with Cutaneous Metastases

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Metastatic lesions to the skin are a recognised but infrequently occurring manifestation of visceral malignancy. The prostate gland only rarely acts as a primary source for cutaneous metastases. The following cases are examples of this unusual presentation of carcinoma of the prostate.

Case 1. A 66-year-old Caucasian farmer was admitted to the Urological Service of the McGuire Veterans' Administration Hospital with adenocarcinoma of the prostate diagnosed 2 years earlier at another institution where he



Fig. 1. Metastatic cutaneous lesions from carcinoma of the prostate covering lower abdomen and right thigh.

had been treated with transurethral resection, bilateral orchidectomy, and stilboestrol. He did relatively well until the present admission when he was hospitalised for pain in the lumbar spine, secondary to osseous lesions. Physical examination was remarkable due to the presence of multiple violaceous, weeping, nodular lesions over the lower abdomen and both anterior thighs. The largest lesion was approximately 4 × 6 cm (Fig. 1). Biopsy sections revealed undifferentiated carcinoma compatible with the primary noted previously in the prostate (Fig. 2). The patient became progressively uraemic secondary to bilateral ureteral obstruction and expired 6 months after admission.

Case 2. A 59-year-old Negro carpenter presented with symptoms of vesical outlet obstruction. Examination revealed an enlarged firm prostate. Cystoscopy demonstrated trilobar hypertrophy and needle biopsy showed poorly differentiated adenocarcinoma of the prostate. The patient underwent transurethral resection of the prostate and bilateral orchiectomy. Within 6 months he had developed severe bone pain secondary to metastatic lesions. At this time he was noted to have multiple nodular lesions of the skin and scalp. Biopsy of these nodules revealed infiltrating poorly differentiated adenocarcinoma compatible with the primary in the prostate (Figs. 3 and 4). The patient's condition deteriorated rapidly and he expired 10 months after the initial diagnosis. Post-mortem showed adenocarcinoma of the prostate with metastases to retroperitoneal lymph nodes, pleural cavities, pericardium, heart and pancreas.

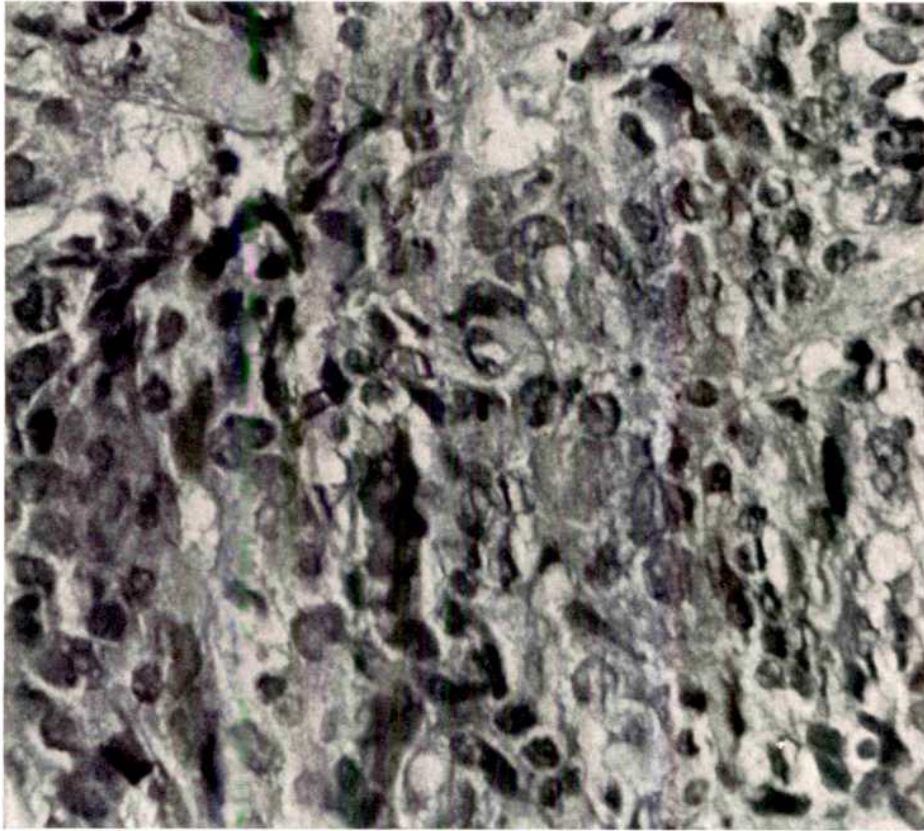


Fig. 2. Case 1. Biopsy section of skin lesion showing adenocarcinoma of the prostate ($\times 930$).

Comment

An extensive search of the literature reveals only 25 instances of cutaneous metastases from a primary source in the prostate. Of these, only 14 are well documented and but 5 appear in the English literature. Ronchese, in 1940, reported a patient with carcinoma of the prostate metastatic to the scalp. In 1957, Bluefarb, commenting on the rarity of cutaneous metastases from the prostate, reported 2 cases with a zosteriform distribution. In 1962, Ichikawa described a patient with bilateral testicular and widespread cutaneous metastases. Tan, in 1971, reported a patient with preputial metastases. Of these 5 patients, 1 expired at 2 months, 1 at 9 months and the third at 10 months after the appearance of skin metastases. Information with which to calculate this interval was not available for Bluefarb's first patient and Tan's patient died of unrelated causes

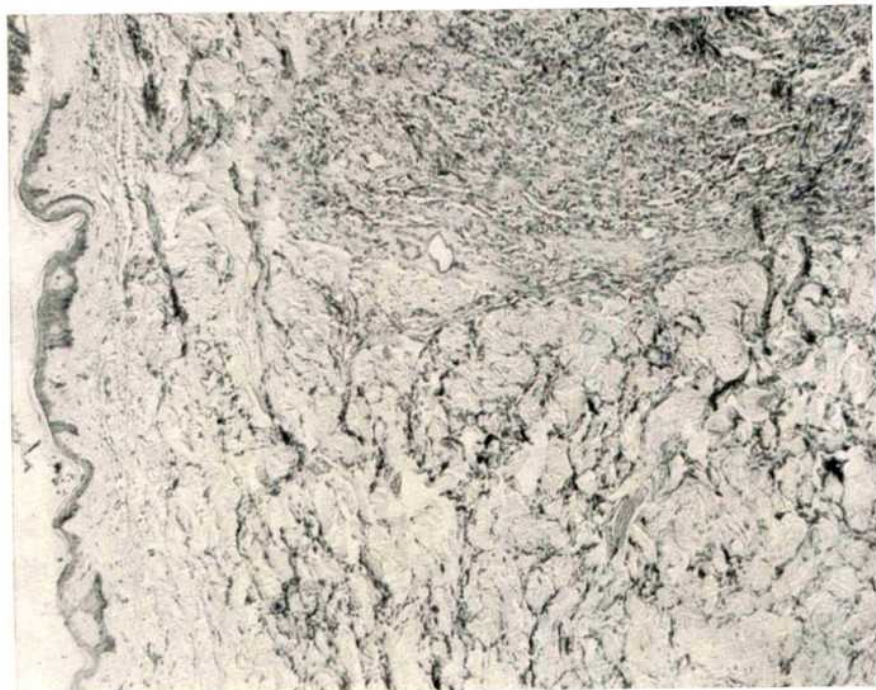


Fig. 3

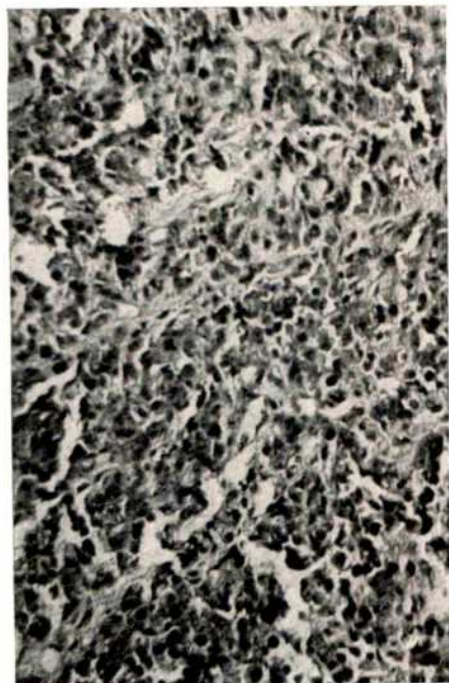


Fig. 4

Fig. 3. Case 2. Adenocarcinoma of the prostate invading dermal and epidermal layers ($\times 100$).

Fig. 4. Case 2. Adenocarcinoma of the prostate as seen in fig. 3 under greater magnification ($\times 430$).

2 months after diagnosis. The 2 patients we have described expired 19 months and 3 months after demonstrating skin metastases. When dates were available in the foreign literature to define the interval between appearance of skin metastases to death, this period never exceeded 1 year. The brief survival after the appearance of cutaneous metastases indicates that they are an expression of an advanced form of prostatic cancer and that they herald an ominous prognosis.

The possible routes of metastases are, of course, venous, lymphatic and arterial. In our opinion the widespread distribution of lesions suggests haematogenous dissemination of tumour emboli.

Summary

Metastatic lesions to the skin are a rare manifestation of prostatic malignancy. Only 14 patients with cutaneous metastases are well documented in the literature to date. Two additional cases are herein included.

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Strontium-87m and the Gamma Camera in the Study of Bone Metastases from Carcinoma of the Prostate

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Carcinoma of the prostate is the commonest form of malignancy affecting the male urogenital tract. An average of 10 men a day die from this disease in England and Wales (Fergusson, 1970). The choice of therapy is a diverse one, ranging through none for many cases of incidentally found Stage A carcinoma, total prostatectomy for Stage B, radiotherapy for Stage C, and endocrine therapy for Stage D metastatic disease (Rubin 1969*a*). Improvements in the results of treatment depend upon more accurate staging; and the early detection of metastases is of major importance. This communication reports experience in the use of strontium-87m (^{87m}Sr) and the gamma camera in the study of metastatic bone lesions from carcinoma of the prostate.

Method

No special preparation was given to the patients before scintigraphy. The investigation was performed at approximately 10 a.m. following a normal breakfast. 1.7 millicuries of ^{87m}Sr was injected intravenously 30 minutes before scintigraphy. This dosage is sufficient to give good quality scintigrams and can safely be repeated for subsequent examinations without irradiation risk to the patient. Estimates of whole body irradiation range from 12 mR (Spencer *et al.*, 1967) to 38 mR (Charkes *et al.*, 1964). Bone exposure estimates range from 168 mR (Charkes *et al.*, 1964) to 690 mR (Meckelnburg, 1964). ^{87m}Sr was chosen in preference to fluorine-18 (^{18}F) because of its widespread availability and its more suitable gamma energy (388 KeV) for the gamma camera.

Immediately before scintigraphy the patients were instructed to empty their bladders. The first scintiphotos taken were of the pelvic area. The camera exposure depended to some degree on the activity of uptake but generally included between 100,000 and 200,000 counts. Further scintigrams were taken of the lumbar and dorsal spine, the upper femoral shafts, and the upper humerus, scapula and clavicle. Other areas were investigated only when there was a clinical or radiographic indication.

Results

71 patients have been studied. 42 of these were patients first investigated before any form of treatment. The investigations were performed in a 4-bedded ward and clinic devoted entirely to the study of carcinoma of the prostate. The diagnosis was confirmed in every case by the histology of Vim Silverman needle biopsies or the cytology of Franzen needle aspirates of the prostate. Every patient had radiographic skeletal survey studies and serum acid and alkaline phosphatase estimations. Positive scintigrams due to metastases with negative radiographic changes were confirmed by biopsy (2), post-mortem examination (1), or by subsequent diagnostic X-ray appearances. During the analysis of results doubtful X-rays and indeterminate scintigrams were both classified as negative. Table I gives an analysis of the total experience in this trial:

Table I

Number of patients investigated	71
Number of patients with metastases	26 (38%)
Number of untreated patients investigated	42
Number of untreated patients with metastases	18 (43%)
Number of patients with repeated investigations	31
Number of scintigrams	120

The uptake of isotope associated with osteolytic lesions was much greater than that associated with osteosclerotic lesions. In general a satisfactory response to treatment was shown by increased calcification and sclerosis on X-ray examination and less well defined uptake of isotope on scintigraphy. Figure 1 demonstrates these changes in a patient treated for 6 months with stilboestrol, 1 mg t.d.s. Different lesions in the same patient may show different degrees of "activity" both on X-ray and scintigraphy. Several patients on treatment had well defined sclerotic lesions on X-ray with virtually no increased uptake of isotope on the scintigram. The change from an osteolytic lesion with marked isotope uptake to an osteosclerotic lesion with little uptake usually took several weeks or months.

Regions which do not show up clearly on X-rays due to overlapping bone or other opacities, can fail to demonstrate the presence of secondaries. Figure 2 shows an example of such a region where the secondary deposits are clearly demonstrated only in the scintigram.

Table II gives in detail the results obtained in 42 patients untreated before the first investigation:

18 of the 42 untreated cases had metastases when first seen, an incidence of 43 per cent. Five of these cases were diagnosed on scintigrams before definite radiographic change (12 per cent). 16 of the 18 cases with metastases had elevated serum acid and alkaline phosphatase levels when first seen, and in 2 the serum concentration of both enzymes was normal. No metastases were found in patients with an elevated serum acid phosphatase only. One patient had an elevated serum alkaline phosphatase and this was associated with a positive scintigram due to Paget's disease.

Nine new patients have been followed up for more than 6 months with repeated scintigrams and 4 of these showed less isotope uptake after treatment (Table III).

Discussion

A considerable change has to take place in normal bone before a metastatic lesion is demonstrable on conventional P-A or lateral radiographs. Borak (1942) has shown experimentally that 30-50 per cent of the substance of a human vertebra, a common site for osseous metastases, has to be removed before a definite diagnosis can be made by X-rays, unless the site of the lesion is suspected and tomography is employed. Many series have shown that bone-seeking isotopes can identify the site of osseous lesions on carcinoma of the prostate before radiography (Faber *et al.*, 1967; Morgan and Mills, 1968; Kontturi and Kivinitty, 1971; Roy *et al.*, 1971). In human bone strontium replaces calcium in hydroxyapatite both by absorption on to the mineral crystal and incorporation into the lattice (Schoenberg, 1963; Charkes and Sclaroff, 1965). Strontium-87m has a relatively short half-life with the advantage of small exposure of the patient to irradiation hazards so that repeated investigations are possible. Unlike fluorine-18 it does not have to be used at special centres which have a cyclotron, because it can be purchased in a generator which will supply adequate isotope for repeated investigations for a period of 1 week or more.

The isotope is taken up by the immature osteoid tissue, or reactive bone, which is produced by the host along new vascular channels around and within active bone lesions. Therefore, scintigraphy is not specific for osseous metastases, but will demonstrate all active bone lesions *e.g.* Paget's

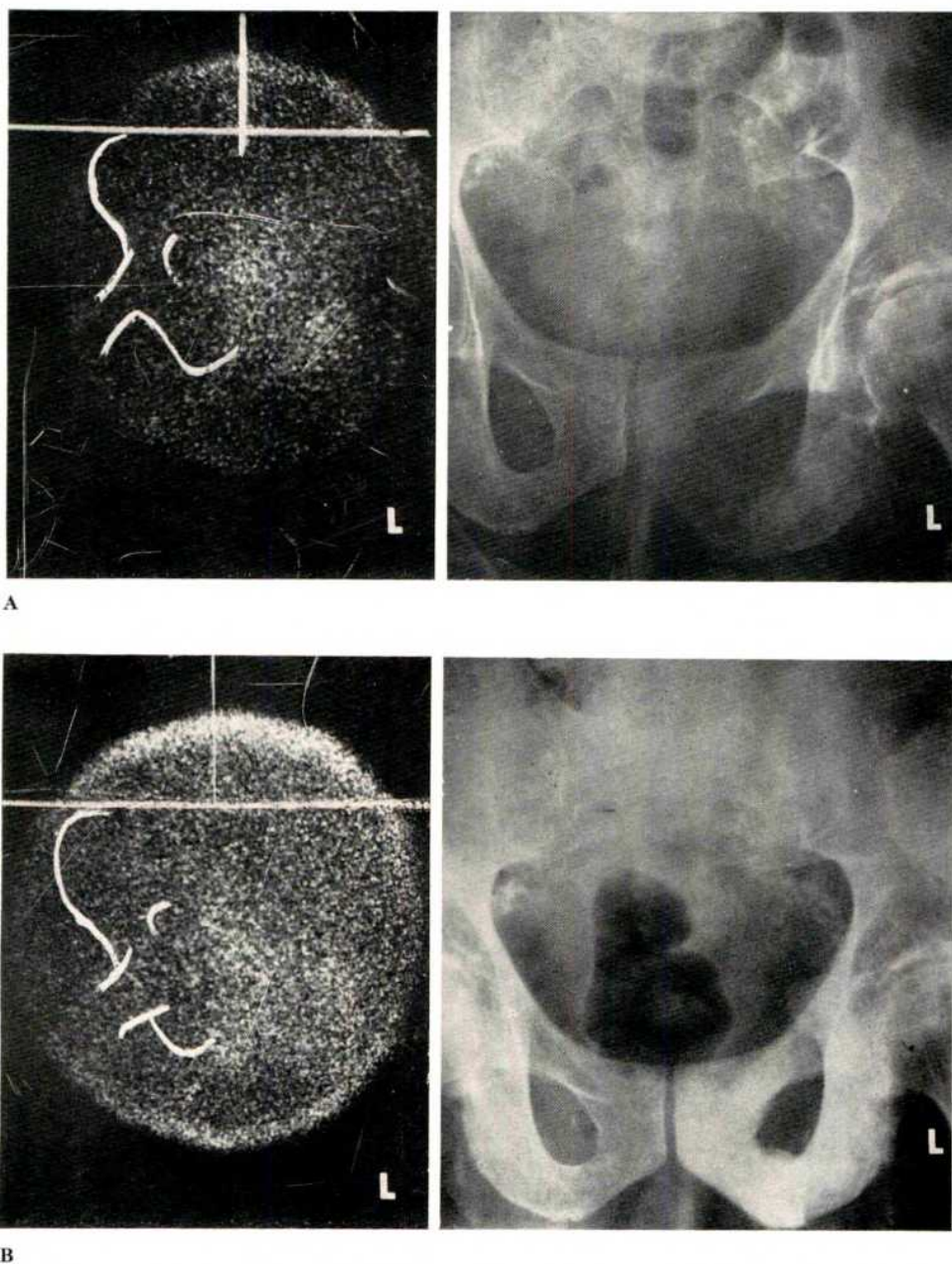


Fig. 1. Pelvic scintigrams and X-rays before and during oestrogen therapy. **A**, 2.2.70 showing an area of positive strontium uptake in the L inferior ischial ramus corresponding to an osteolytic metastasis on the X-ray. **B**, 12.1.71 showing a reduced strontium uptake in the L ischium area associated with an osteoblastic change on the X-ray after treatment.

disease, osteomyelitis, healing fractures or growing epiphyses in children. The diagnosis has to be confirmed by a biopsy or subsequent radiographic change. When the lesions are brought under control by treatment the osteoid tissue calcifies and loses its avidity for the isotope (Galasko and Doyle, 1970). Thus sclerosis of lytic lesions on X-ray suggests partial or complete healing, and is

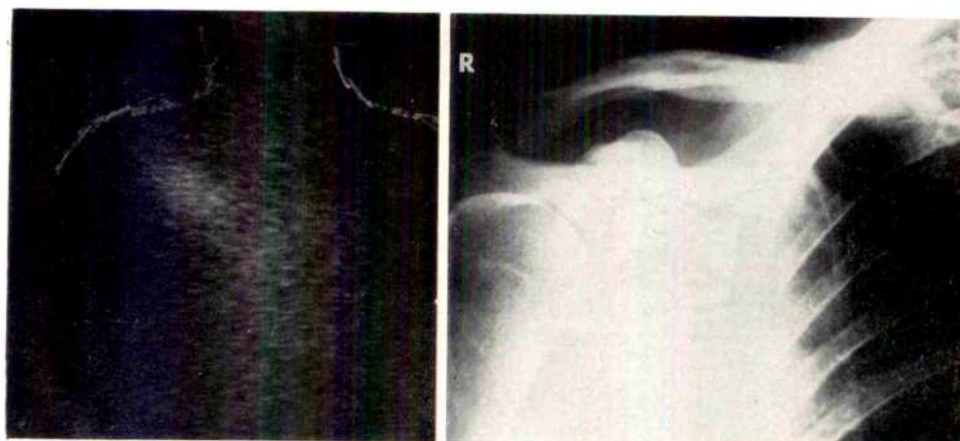


Fig. 2. 27.4.70 Scintigram showing an area of positive uptake in the R clavicular region. No corresponding area could be seen on the X-rays due to the bone overlapping in the region of the lesion. The metastasis was confirmed by biopsy.

Table II

	Positive Skeletal Survey	Positive Scinti- graphy	Negative Skeletal Survey	Negative Scinti- graphy	Comments
Normal SAP } Normal SalkP }	1	2	16	15	2 Metastases/1. Diagnosed before X-ray
Elevated SAP only	0	0	7	7	0 Metastases
Elevated SalkP only	0	1	1	0	1 Paget's disease
Elevated } SAP } Elevated } SalkP }	12	16	5	1	16 Metastases/4. Diagnosed before X-ray
Total	13	19	29	23	5 Metastases. Diagnosed before X-ray

SAP = Serum acid phosphatase. SalkP = Serum alkaline phosphatase.

Table III

Number of patients with metastases followed up for more than 6 months after commencing treatment	9
Number of patients showing less activity on repeat scintigrams	4

represented by diminished or absent isotope uptake on the scintigram. Repeated scintigraphy with short half-life isotopes enables us to view metastases in a dynamic rather than a static fashion (Rubin, 1969b) and gives us some indication of the patient's response to treatment. These changes take several weeks to appear both on X-ray and scintigraphy, comparable with the laying down of callus by healing fractures. Conversely relapsing and painful progressive lesions show a very marked isotopic uptake on scintigrams. Greenberg *et al.*, (1966) have observed that isotope uptake is not likely to be as marked in slowly progressive lesions like those of carcinoma of the prostate as in more active lesions such as those from carcinoma of the breast. All these factors have to be considered when comparing scintigraphic and X-ray findings.

The gamma camera has an advantage over the scintiscanner in that it produces rapid polaroid photography with little inconvenience to the elderly patient with carcinoma of the prostate. However, the localisation of the lesion is crude, and at present there is no satisfactory way of taking quantitative measurements of isotope uptake.

In addition the comparison of scintigrams taken at different times in the same patients presents many problems. In our series the display tube focus, spot brilliance and astigmatism, and camera f/number were normally set at the same values. Occasionally variations of the display necessitated varying these parameters to obtain comparable pictures. Long-term comparisons are difficult to assess because of variations in the quality of polaroid film and also in the metabolism of strontium by the patient. No attempt has been made in this study to quantitate the uptake of isotope in active bone compared with normal bone or with the general tissue background. However, despite these obvious limitations, visual evaluation of scintigraphy rarely conflicted with the X-ray and clinical findings.

Conclusions

Our initial experience indicates that if a new patient with carcinoma of the prostate presents with elevation of both the acid and alkaline serum phosphatases above normal levels skeletal survey radiography is indicated. If this fails to show metastases there is then a definite place for scintigraphy. The localisation of possible metastases for tomography, biopsy or local radiotherapy is not yet as accurate with the gamma camera as with the conventional scan. However, a positive gamma camera scintigram in a patient with proven carcinoma of the prostate can be a useful guide to the clinician in planning therapy.

Summary

Bone-seeking isotopes can identify the site of osseous lesions in carcinoma of the prostate before radiography.

The use of strontium-87m and the role of gamma camera scintigraphy in a series of 71 cases of carcinoma of the prostate is discussed.

The value of strontium-87m scintigraphy is seen not only in its ability to detect some lesions earlier than radiological methods, but also as a parallel investigation which enhances overall diagnostic reliability.

Repeated investigations are capable of providing some additional indications of the patient's response to treatment.

The limitations of the scintigraphic method in repeated examinations are discussed.

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Prostatic Disease in the Leukaemic Patient—with Particular Reference to Leukaemic Infiltration of the Prostate—a Retrospective Clinical Study

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Leukaemic infiltration of the prostate (Figs. 1-4) is uncommon. Watson, Sauer and Sadugor (1949), in their review of 1,073 cases of lymphomata, found 3 instances of lymphosarcoma involving the prostate but described no case with leukaemic infiltration. Since Jacobi, Panoff and Herzlich (1937) first reported a case of infiltration of the prostate by lymphatic leukaemia, 13 further cases have been published (Flaherty, Cope and Shecket, 1940; Lubin, Fetter and Erf, 1947; Hare, Spence and Fuqua, 1949; Connor, Heinemann and MacNish, 1950; Johnson and Gundersen, 1953; Tighe, 1960; Entz and Kruse, 1961; Fishman and Taylor, 1963; Vinnicombe, 1963) making a total of 14 cases in all. 11 of these had chronic lymphatic leukaemia and the remaining 3 had monocytic leukaemia.

The object of this paper is to report our experience with leukaemic patients who developed prostatic obstruction—referring particularly to those with leukaemic infiltration of the prostate.

Patients

In a consecutive series of 4,863 prostatectomies at the Urological Department, Meath Hospital, during the years 1955-70 inclusive, 6 instances of leukaemic infiltration of the prostate occurred; 3 of these patients have been briefly reported elsewhere (O'Flynn, 1966). This is an incidence of less than 0.1 per cent. The main clinical features are summarised in Table. In addition to our 6 leukaemic patients with leukaemic infiltration of the prostate, 8 other patients with leukaemia and prostatic obstruction—but without leukaemic infiltration of the gland—were seen, illustrating that leukaemia does not, inevitably, involve the prostate.

Patients with Leukaemic Infiltration of the Prostate

Five of the 6 patients were in the 8th decade: 1 man was aged 57. In 4 patients the leukaemia was diagnosed pre-operatively, and in the remaining 2 the diagnosis was made on histological examination of the prostate. In this group of patients, all had chronic lymphatic leukaemia. The duration of prostatic symptoms was variable: 4 patients had had symptoms of prostatic obstruction for a year, or longer. Analysis of their symptoms revealed no specific clinical pattern to distinguish patients with leukaemic infiltration of the prostate from those with benign glandular hyperplasia. Physical examination of the prostate in these 6 patients was unremarkable; only 1 patient (F. S.) was thought to have a prostate of abnormal consistency. All 6 patients underwent transurethral prostatectomy, 4 by diathermy electro-resection and 2 by cold-punch resection. The amount of tissue resected ranged from 3 to 53 g, the average weight being 21 g. During resection there were no characteristic endoscopic features of the prostate with leukaemic infiltration. All patients made an uneventful postoperative recovery without an unusual amount of prostatic bleeding. Three patients received 1 unit of blood: the others did not require transfusion.



Fig. 1. Round cell infiltration of benign hyperplastic prostate in chronic lymphatic leukaemia ($\times 100$).

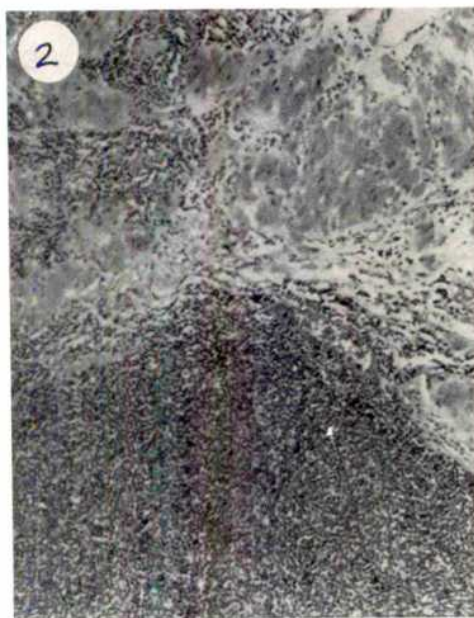


Fig. 2. Massive leukaemic infiltration of prostate. Benign hyperplasia of prostate present in upper $\frac{1}{2}$ of slide ($\times 40$).

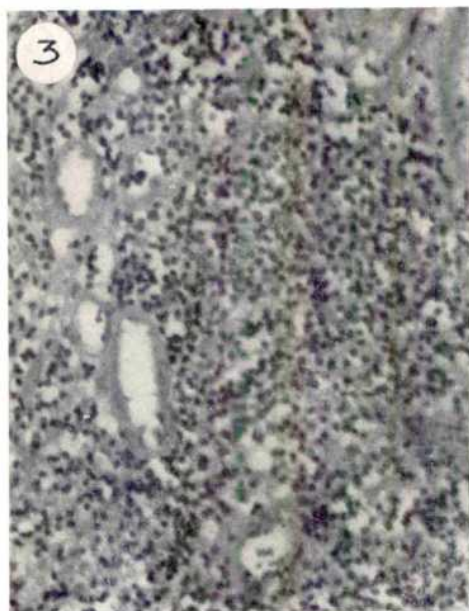


Fig. 3. Diffuse round cell infiltration of prostate. No obvious prostatic tissue seen ($\times 100$).

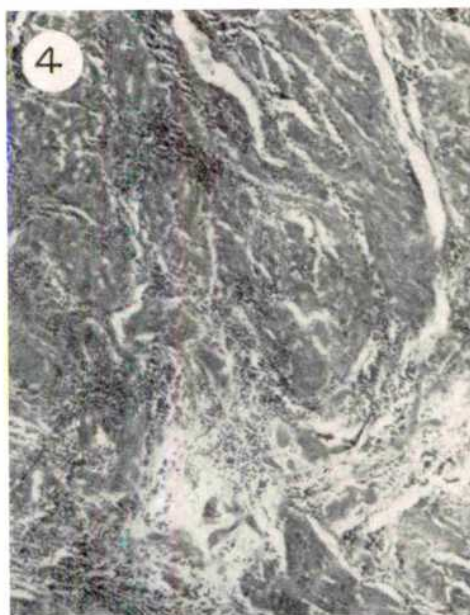


Fig. 4. Scattered focal areas of leukaemic infiltration in benign hyperplastic prostate ($\times 40$).

Table

Name	Age	Duration of Symptoms	Prostate	Diagnosis	Histology	Postoperative Recovery	Subsequent Course
1. P. D.	71	3 weeks: Haematuria frequency	Mod. enlarged	<i>Pre-op.:</i> Chronic lymphatic leukaemia Platelets 135,000. No bleeding defect. W.C.C. 160,000	TUR—35 g. Massive infiltration by lymphocytes. (February 1962)	Uneventful. 1 unit blood given	Alive and well 2 years later
2. F. S.	74	1 year: Haematuria, frequency and dysuria	Slightly enlarged and firm (?calculus prostatitis).	<i>Post-op.:</i> Lymphatic leukaemia	TUR—15 g. Heavily infiltrated by lymphocytes. Suggestive of lymphatic leukaemia (March 1970). Bladder biopsy, October, 1971. Transitional cell carcinoma infiltrating muscle	Uneventful	Died 9.11.71. 19/12. <i>Autopsy:</i> Transitional cell carcinoma; obstruction left kidney and pyonephrosis; generalised chronic lymphatic leukaemia
3. M. F.	76	1 year: Difficulty of micturition, leading to retention	Enlarged. Normal consistency	<i>Pre-op.:</i> Chronic lymphatic leukaemia. W.C.C. 127,500 Platelets 185,020	TUR—53 g. Adenomatous hyperplasia with marked lymphatic infiltration (August 1963)	Uneventful. 1 unit blood given	Alive and well 2 years later
4. J. G.	70	1 year: Frequency nocturia and weak stream	Normal size and consistency	<i>Post-op.:</i> Chronic lymphatic leukaemia	Punch resection—3 g. (February 1962). Diffuse, massive infiltration by lymphocytes. Lymphatic leukaemia	Uneventful	Repeat resection March 1966. Died July 1966
5. J. P.	57	Approx. 5 years: Slow stream 1/52 haematuria	Prostate normal size and consistency	<i>Pre-op.:</i> Chronic lymphatic leukaemia. Generalised adenopathy	Punch Resection—5 g. (February 1956). Massive infiltration of prostate by lymphatic leukaemia	Uneventful. 1 unit blood given	Lost to follow-up
6. D. B.	72	1 week: Haematuria, frequency and nocturia. Overflow incontinence R.U. 1,200	Enlarged. Normal consistency	<i>Pre-op.:</i> Chronic lymphatic leukaemia	TUR—16 g. (October 1970). Benign hyperplasia with lymphocytic infiltration	Uneventful	Alive and well 2 years later

Case 2, (F.S.), is of particular interest because of the occurrence of 2 malignancies in his lower urinary tract. He was admitted with prostatic symptoms of 1 year's duration. He underwent a transurethral resection of his prostate, and a diagnosis of leukaemia was made on the histological appearance of his prostate. The diagnosis of chronic lymphatic leukaemia was confirmed by further study of his bone marrow and peripheral blood and he was given a course of 6-fluorouracil. He made a satisfactory postoperative recovery from the prostatectomy but returned a year later with symptoms of intense frequency and dysuria. This time cystoscopy was negative. He was discharged on antibiotics and antispasmodics. He returned 3 months later with the same complaints and was found to have developed a vesical neoplasm. Endoscopic biopsy revealed a transitional cell carcinoma with extensive muscle involvement. The patient died a few weeks later and post-mortem confirmed the presence of both malignant processes.

Leukaemic Patients with Prostatic Obstruction, but no Leukaemic Involvement of the Prostate

Eight patients fell into this category and presented to the Urological Department with acute retention. All 8 patients were known to have leukaemia before admission. The urological history and examination of these patients was unremarkable. Six of the 8 patients had chronic lymphatic leukaemia, all of whom underwent uneventful resection of the prostate. One patient had chronic myeloid leukaemia. He was admitted in retention and was found to have, in addition to his leukaemic process, a bronchogenic carcinoma of the lung. His general condition precluded surgery and he died shortly after admission. The remaining patient had acute myelomonocytic

leukaemia and underwent transurethral resection. Post-operatively he required 3 units of blood but otherwise made an uneventful recovery.

All patients known to have leukaemia were screened for haemostatic defects. The tests were negative in all cases and the platelet counts were normal.

Discussion

Both in their clinical presentation and response to prostatic surgery there seems to be little difference between patients with leukaemic infiltration of the prostate and those with benign glandular hyperplasia. One patient, (F. S.), was found to have abnormal physical findings of the prostate. In the remaining 13 patients, clinical examination was unremarkable, which raises the question of the role of leukaemic infiltration of the prostate in the production of obstructive prostatic symptoms. Meyer (1941) thought that there were 2 types of leukaemic infiltration of the prostate: a symptomless variety with no obstructive features, generally occurring in younger patients, and a variety in older men in which leukaemic infiltration of the prostate is present in association with benign glandular hyperplasia. It would appear from a study of our 6 cases that infiltration of the prostatic gland occurs in a substantial number of patients with leukaemia, but probably contributes little to the development of urological symptoms. It seems probable that prostatic obstructive symptoms in these cases are due to benign glandular hyperplasia and that the finding of leukaemic infiltration is an incidental and non-contributory factor in the development of urological symptoms. Chronic lymphatic leukaemia is a disease of the elderly and it is to be expected that two disease processes which occur in this age group will occasionally co-exist, but it is unlikely that one disease process influences the other in the production of urinary obstructive symptoms.

Of greater interest is the systemic effect of leukaemia on the patient undergoing prostatectomy. As one would expect, the type of leukaemia is important, not only in the general outcome for the patient, but also with regard to the clinical management after prostatectomy. 12 of the 14 patients in our series had chronic lymphatic leukaemia, and this includes the 6 patients with leukaemic infiltrations of the prostate. All 12 patients had transurethral resection of the prostate and made an uneventful postoperative recovery. In particular, no patient had significant bleeding in the postoperative period; less than half required 1 unit of blood. Of the remaining 2 patients, 1 had chronic myeloid leukaemia and was unfit for prostatectomy because of his poor general medical state. The remaining patient had acute myelomonocytic leukaemia. He had a 35-g resection and required 3 units of blood postoperatively, but otherwise made a satisfactory recovery.

Of the 14 patients previously reported, 11 had chronic lymphatic leukaemia. The remaining 3 had acute monocytic leukaemia (Flaherty, Cope and Shecket, 1940; Lubin, Fetter and Erf, 1947; Tighe, 1960). Of the 11 patients with chronic lymphatic leukaemia, 10 had surgical treatment and 1 patient had radiotherapy. The majority of the surgical procedures were uneventful and haemorrhage occurred in only 1 patient during operation. One patient (Vinnicombe, 1963) required 8 units of blood in the postoperative period following retropubic prostatectomy and clot was evacuated from the bladder on two occasions. The remaining patient, treated conservatively, had local irradiation of the prostate (Fishman and Taylor, 1963) and satisfactory micturition was re-established. Of the 3 patients with acute monocytic leukaemia, 2 had surgical treatment (Flaherty, Cope and Shecket, 1940; Lubin, Fetter and Erf, 1947). The patient reported by Flaherty *et al.* (1940) underwent transurethral resection of the prostate and made an uneventful postoperative recovery. He then had irradiation to his prostate and developed an acute bleeding episode, from which he subsequently died. Lubin *et al.* (1947) described a patient who had a severe haemorrhage in the postoperative period which required packing of the prostatic cavity. He was left with a permanent suprapubic cystostomy and was discharged from hospital after a prolonged and stormy postoperative convalescence. The patient reported by Tighe (1960) was admitted with acute retention and died from congestive cardiac failure before coming to operation.

Conclusions

In patients with leukaemia who develop urological symptoms, a significant percentage will be found to have leukaemic infiltration of the prostate. The occurrence of leukaemic infiltration of the prostate produces no specific symptom complex or characteristic physical finding. The diagnosis is established on histological examination of the prostate. Patients with chronic lymphatic leukaemia who develop prostatic obstruction require no special urological management. Obstructive symptoms occurring in a leukaemic patient may be dealt with on their own merits and the standard management for any obstructing prostate instituted. While patients with more virulent forms of leukaemia tend to be poorer operative risks, in general leukaemic patients, especially, those with chronic lymphatic leukaemia, withstand prostatic surgery well and have a post-operative course similar to those undergoing prostatectomy for benign glandular hyperplasia. Special methods of treatment directed locally against leukaemic infiltration of the prostate, such as radiotherapy or chemotherapy (Entz and Kruse, 1961) seem unnecessary and on occasions may precipitate complications, such as bleeding (Flaherty, Cope and Shecket, 1940). Specific treatment of the leukaemic process is indicated entirely on medical grounds and need not be instituted in anticipation of postoperative bleeding.

Summary

14 leukaemic patients with obstructive prostatic symptoms are reported. Six cases had leukaemic infiltration of the prostate.

13 patients underwent prostatectomy, which was uneventful in all cases.

Leukaemic infiltration of the prostate produces no characteristic symptoms or physical findings. It could not be considered a clinical entity and is of academic interest only.

We wish to thank Mr Victor Lane, who treated some of these cases, for his co-operation.

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Leukaemic Infiltration of the Prostate in a Patient with Chronic Lymphatic Leukaemia—a Case Report

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Chronic lymphatic leukaemia is primarily a disease of old age, and in 25 per cent of patients is discovered in an asymptomatic stage during a routine examination for an unrelated disease.

Exceptionally localised leukaemic infiltration may produce unusual manifestations of the disease.

Case Report

H. A., aged 68, was seen in the Haematology Clinic at the Northern General Hospital, Sheffield on 12th May 1971, with a 6-week history of generalised lymph gland enlargement. There were discrete non-tender glands in the neck, axillae and groin and a moderate degree of hepatosplenomegaly. Rhonchi were heard at the base of the right lung. No other abnormal findings were elicited. Laboratory tests were as follows: haemoglobin 12.5 g per 100 ml; W.B.C. 60,000 per cu mm; differential count—neutrophils 3 per cent, lymphoblasts 3 per cent, lymphocytes 94 per cent; reticulocytes 1 per cent; platelets 180,000 per cu mm; bone marrow aspirate—a cellular sample of marrow showing a large excess of lymphocytes and a small number of lymphoblasts, megakaryocytes present; uric acid 6.1 mg per cent; urea and electrolytes and liver function tests were normal. A diagnosis of chronic lymphatic leukaemia was made, but specific treatment was not considered necessary.

He was admitted as an emergency on 15th June 1971 following a 3-day period of mental confusion, with a right lower lobe pneumonia. Whilst undergoing treatment for this, he developed acute retention of urine and was transferred to the University Department of Surgery, where an indwelling Foley catheter was easily inserted.

It was then found that he had a 6-month history of poor urinary stream with hesitancy, terminal dribbling and frequency of micturition, but no haematuria. On rectal examination the lateral lobes of the prostate were symmetrically enlarged and firm, but the median groove was preserved. The serum acid phosphatase was normal. An intravenous pyelogram showed no intrinsic lesion of the urogenital tract, though the ureters were deviated from the midline, presumably due to pressure from retro-peritoneal lymph nodes. An X-ray of the lumbo-sacral spine was normal and a catheter specimen of urine was sterile. A tentative suggestion that this might represent leukaemic infiltration of the prostate was made.

Cystoscopy was performed on 9th July 1971. The bladder wall showed early trabeculation and there was a moderate degree of cystitis, most marked on the trigone. The appearance of the prostate was of benign hyperplasia; 22 grams of prostate were resected without difficulty or undue bleeding. Following resection, he quickly regained excellent control of urine and was discharged home on 21st July 1971. He was seen 3 months later in the out-patient department and had no symptoms referable to the prostate and no difficulties with micturition.

The histology of the prostate gland was reported as follows: "There is some mild benign hyperplasia with a few simple cysts, but the overwhelming feature is a diffuse lymphocytic infiltration typical of lymphatic leukaemia. There is no evidence of infection or prostatic carcinoma." (See Fig.).

Comment

11 cases of infiltration of the prostate in chronic lymphatic leukaemia have been reported in the world literature (Jacobi, Panoff and Herzlich, 1937; McCrea, 1940; Hare, Spence and Fuqua, 1949; Connor, Heinemann and MacNish, 1950; Johnson and Gundersen, 1953; Entz and Kruse, 1961; Fishman and Taylor, 1963; Vinnicombe, 1963).

Only 3 patients, as in the present case, were known to have chronic lymphatic leukaemia prior

to admission to hospital. It was the retention of urine and not the general symptoms of leukaemia which brought 7 patients to seek medical advice.

The outstanding histological feature of the excised prostates has been infiltration by sheets of lymphocytes. Although 7 patients gave a history of increasing trouble with micturition of between 1 and 5 years' duration some degree of benign hyperplasia was reported in the specimens from only 4 of them. It seems, therefore, that some patients with chronic lymphatic leukaemia may have mild prostatic symptoms for some years which may eventually culminate in acute retention without there being evidence of benign hyperplasia, despite their belonging to an elderly age group.

Both enucleation and transurethral resection of the prostate appear to have given equally good results. No technical difficulties which could be ascribed to leukaemic infiltration have been

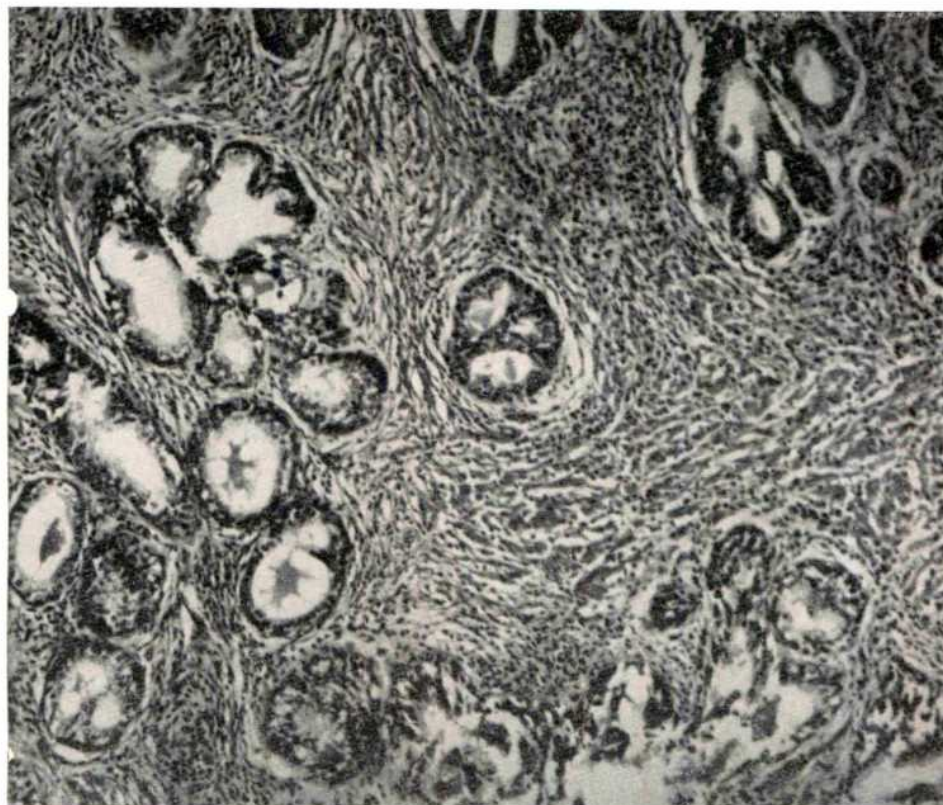


Fig. Prostate gland ($\times 75$.) The outstanding feature is lymphocytic infiltration.

recorded. Five glands were enucleated and of these only 1 bled excessively whilst, as in our case, no immediate complications were reported in the 5 glands resected transurethraally.

The place of local radiotherapy in treatment cannot be assessed as only 1 case was treated by this method: Fishman and Taylor (1963) treated 1 case with local low-dosage radiotherapy and reported the patient was voiding well 6 weeks after treatment.

Summary

A case of chronic lymphatic leukaemia with leukaemic infiltration of the prostate and acute retention of urine is described.

Brief comments are made on certain features of 11 previously reported cases.

I wish to thank Professor F. J. P. O'Gorman, Honorary Director of the University Surgical Unit, Northern General Hospital, for permission to report this case.

I also thank Dr P. Day, Senior Registrar in Pathology, Northern General Hospital, for the histology report and Mr C. A. Lambourne, Chief Technician, for producing the photographs.

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The Evaluation of Prostate Size by Ultrasonic Scanning : a Preliminary Report¹

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In the investigation of bladder outlet obstruction due to prostatic disease, accurate assessment of the size of the prostate gland is important so that the best operative procedure, either open prostatectomy or endoscopic resection, is selected. Difficulties can arise at open operation when the gland is found to be much smaller than expected. On the other hand, if the size is underestimated a prolonged endoscopic resection may be undertaken with all its attendant risks (Kidd and Burnside, 1965).

The methods in current use to investigate the size of the prostate gland include digital examination, endoscopy with bimanual examination and contrast radiography. These methods are not precise and can give erroneous results (O'Flynn, 1969). A technique for measuring prostatic weight using retrograde cysto-urethrography has been described (Thumann, 1951). However, with this technique, which is very elaborate, the measurement error is about 20 per cent.

We have developed and investigated the use of an ultrasonic scanning technique as a method of measuring the size of the prostate gland prior to operation.

Brief Theory of Ultrasonic Scanning

When a short pulse of ultrasound is directed into the body via a transducer which acts as both transmitter and receiver, reflected pulses (echoes) are received from interfaces between tissues having different acoustic properties. The degree of reflection is a function of the difference in value of the relative acoustic impedances on each side of the interface, acoustic impedance being defined as the product of the tissue density and the velocity of sound in the particular tissue.

The echoes received at the transducer are converted to weak electrical signals which are amplified, electronically processed, and finally displayed on a cathode-ray tube, either in the form of vertical deflections from a horizontal reference—*i.e.* amplitude modulation (A-scan), or in the form of small spots correctly orientated relative to their source of origin in distance and angle from the transducer—*i.e.* brightness modulation (B-scan). The overall "picture" in 2 dimensions is obtained by compounding many individual B-scan results in a smooth "section scanning" action.

Methods

For ultrasonic scanning of the prostate gland no preliminary preparation of the patient is required except that he is requested to withhold micturition for at least 2 hours before operation. If there is a catheter in the bladder this is clamped for the same length of time. The scan is performed with the patient supine, the transducer being passed over the lower abdomen in both longitudinal and transverse planes. To ensure good acoustic coupling a thin layer of oil is used as a contact medium between the transducer and the skin.

¹This paper is based on a presentation to the Surgical Research Society in January, 1972.

In the longitudinal sections (Fig. 1, A) the outline of the bladder and prostate gland are seen. Full visualisation in this plane is limited by the presence of the pubis, so, for overall assessment of prostatic size and shape, sections taken in the transverse plane are necessary (Fig. 1, B). The benign prostate, as illustrated, appears as a smooth, acoustically homogeneous structure approximating a sphere in outline.

Several scans are made. The scan which shows the largest area of prostate gland is selected and from this scan the volume of the prostate is calculated from the measured diameter. A very large prostate gland (Fig. 2) appears as a bi-lobed structure and for the purpose of measurement of volume, it is calculated as consisting of 2 spheres.

To evaluate ultrasonic scanning as a method of measuring prostatic size 15 patients presenting with benign prostatic enlargement and requiring operation were examined. A surgeon performed a rectal examination and thereafter each prostate gland was placed in one of 3 arbitrary groups, large (6 patients), moderately enlarged (5 patients) and normal (4 patients). All patients had an intravenous pyelogram and a radiologist examined the bladder films for evidence of prostatic enlargement. A physicist, skilled in the use of ultrasonic scanning, calculated the volume of each prostate gland by the method described. When the prostate glands were removed at operation their sizes were determined by weight and volume displacement. At a later date all these findings were correlated and compared.

Results

For the purpose of analysing the results of this investigation we divided the prostate glands into 3 groups depending on the actual volume of prostatic tissue removed at operation. Large prostates are those of 70 cc volume and over, medium-sized prostate glands lie within the volume range 30 cc to 69 cc and small prostates are below 30 cc in volume.

In the group of patients where the prostate glands were considered to be large on rectal examination (Table I), the actual gland volumes were found at operation to vary from 30 cc to 85 cc. This considerable range demonstrates an inaccuracy of rectal examination in estimating the size of the prostate gland. Only 3 of the glands in this group were found to be large by our criteria. Size estimation by X-ray analysis was correct in only 1 patient whereas prostate gland size, as determined by ultrasonic scan, was accurately estimated in each instance.

Digital examination was more accurate in those patients with clinically moderately enlarged prostate glands (Table II). In this group the operative volumes of the prostate glands were within the range 30 cc to 65 cc. X-ray estimation of size was quite inaccurate, only 1 patient being correctly assessed. There was again a close correlation between size as determined by ultrasonic scanning and actual size as determined by volume estimation of the operative specimens.

In the group of patients where the prostate glands were considered to be of normal size on rectal examination (Table III), each patient was treated by endoscopic resection. As a consequence, no operative specimen was available for actual determination of gland size. However, all the resections were of short duration with only between 15 g and 20 g of tissue removed and it is reasonable to assume that all the glands were of small volume. Digital examination was, therefore, accurate in each case in assessing prostate size, as was ultrasonic scanning. X-ray assessment of size was misleading in 1 case.

Discussion and Conclusions

It is possible to draw certain tentative conclusions from the findings of this preliminary investigation into the use of ultrasonic scanning as a means of determining the size of prostate glands before operation.

We found rectal examination to be a reliable means for determining the size of the prostate gland if the gland is small or slightly enlarged. With larger glands, however, the error in size

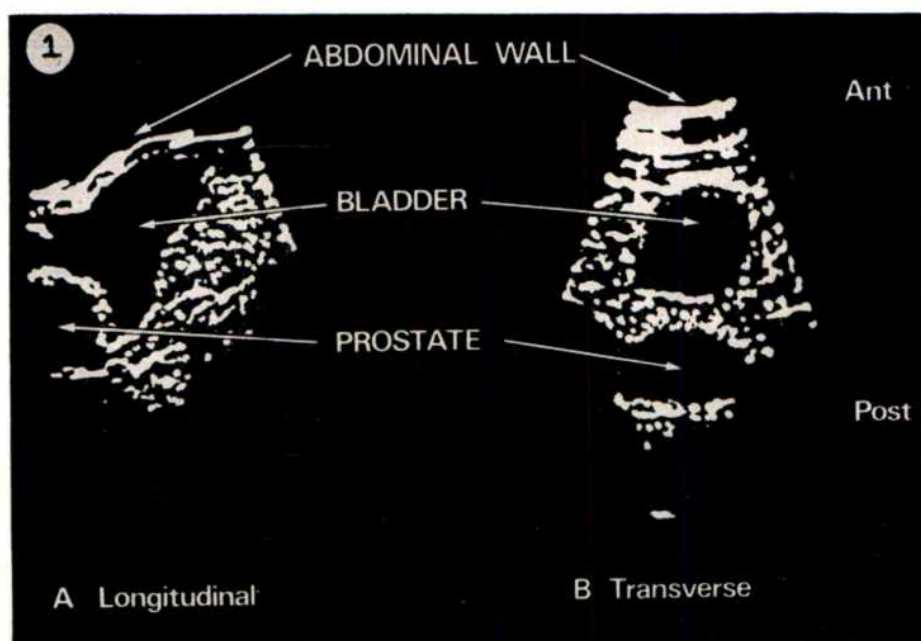


Fig. 1. An ultrasonic scan of the prostate gland and the bladder (B-scan presentation) in the longitudinal plane (A) and transverse plane (B).

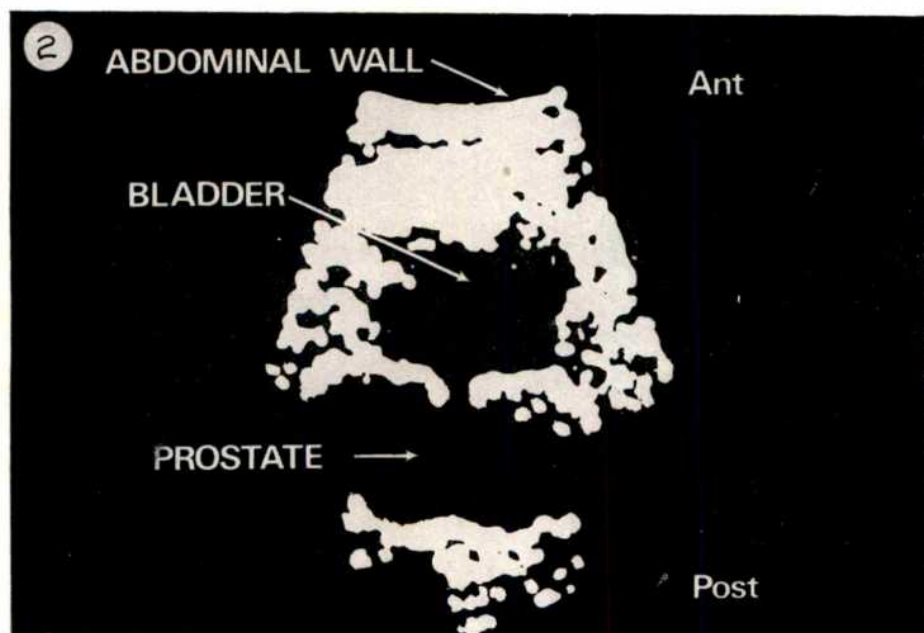


Fig. 2. An ultrasonic scan, in the transverse plane, of a very large, benign, prostate gland (B-scan presentation).

Table I

Size assessment by X-ray and ultrasound analysis of the prostate glands of 6 patients with clinically large prostates. These findings are compared with the actual volumes of the prostate glands removed at prostatectomy

Clinically Large Prostates		
X-ray Assessment	Ultrasound Assessment (cc)	Operative Volume (cc)
Large	86	85
Small	74	75
Small	74	70
Large	32	30
Small	50	45
Large	40	32

Table II

Size assessment by X-ray and ultrasound analysis of the prostate glands of 5 patients with clinically moderately enlarged prostates. These findings are compared with the actual volumes of the prostate glands removed at prostatectomy

Clinically Moderate Size Prostates		
X-ray Assessment	Ultrasound Assessment (cc)	Operative Volume (cc)
Moderate	68	65
Small	45	50
Large	52	40
Large	45	40
Small	32	30

Table III

Size assessment by X-ray and ultrasound analysis of the prostate glands of 4 patients with prostate glands not considered to be enlarged on rectal examination. The actual size of these glands was not determined as each patient was treated by endoscopic resection rather than by open operation

Clinically Normal Size Prostates		
X-ray Assessment	Ultrasound Assessment (cc)	Operative Volume (cc)
Small	20	—
Small	24	—
Small	22	—
Large	35	—

assessment may be considerable. There was an overlap between prostate glands classified as moderately enlarged and those classified as large when the results of size assessment by digital examination were compared with the actual volumes of the prostatic tissue removed at operation. We found that size determination of the prostate gland by analysis of X-ray films of the bladder was quite inaccurate.

Ultrasonic scanning appears to be an accurate method for determining the size of the prostate gland, irrespective of whether the gland is grossly enlarged or only slightly enlarged. It is a simple procedure which can be carried out without discomfort to the patient. We accept that the adenoma removed at operation does not represent the total amount of prostatic tissue. For this reason our findings may not be as accurate as they seem. However, even with this reservation we believe that ultrasonic scanning is the most accurate method currently available for determining the size of the prostate gland before operation.

Summary

The size of the prostate gland in 15 patients presenting with bladder outlet obstruction due to benign prostatic hypertrophy was determined by digital examination, by analysis of the bladder films of intravenous pyelograms and by ultrasonic scanning of the prostates.

It is concluded that ultrasonic scanning is the most accurate method for determining prostate gland size.

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Urethral Calculi

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The management of patients with urethral calculi presents many important problems, and failure to adhere to a correct policy of treatment can result in severe morbid changes in the lower urinary tract. Treatment varies in individual cases, being largely governed by the site and nature of the urethral calculus.

This study is based on the experience of 86 cases of urethral stones treated in the Sabah Hospital, Kuwait, between 1964 and 1972. Further opportunity has occurred to study the problems of presentation and treatment of urethral calculi in a larger series treated in the Emiri Hospital, Kuwait, between 1957 and 1963, and in the University Hospital of Cairo between 1953 and 1957. However, a critical analysis of these cases is not included in this paper.

Table I shows the number, sex and age incidence of the reported series. It is interesting to note that no urethral calculi were encountered in females. The oldest patient was a man aged 62, and the youngest was a boy aged 2 years 9 months, both presenting with acute retention due to impaction of a stone in the posterior urethra. One patient had recurrent impaction of calculi above a urethral stricture on four occasions.

As will be seen from Table II, in only 37 per cent of the cases was the stone located in the posterior urethra, while in 63 per cent it was more distally situated.

There were no other stones in the urinary tract in 67.4 per cent of the cases while in the remaining 32.6 per cent there were other associated calculi (Table III).

Although prevalent in the area where this study was undertaken, bilharziasis was associated with only 30 per cent of the reported series (Table IV). Other lesions of the urinary tract that were associated with urethral stone are shown in Table IV.

Presentation

Acute urinary retention was the mode of presentation in 74 cases (88.9 per cent); frequently the stone was palpable in the anterior urethra or visible at the external meatus. In 8 cases there was a previous history of a recent ureteric colic, apparently followed by the distal passage of the stone and its impaction in the urethra. In some cases the obstruction was partial, but micturition was very painful, with a poor stream and occasional bleeding at the start.

Only in 12 cases (11.1 per cent) was there a non-acute presentation. Figures 1 to 5 illustrate some with specially interesting features.

It is interesting to note that 5 patients had their stones diagnosed only during a repeat, routine X-ray examination for chronic urinary symptoms. In these cases the stones had been missed on previous examination as the films had not included the urethral area.

Diagnosis

A careful history is often suggestive of a urethral calculus. External palpation will reveal the stone if situated in the penile or bulbous urethra. Rectal (or vaginal) examination may detect stones more deeply located.

Table I
Age and Sex Incidence

	No. of Cases	Percentage
Females	0	
Males		
Infants	0	
Children 1-14	12	13.9
Adults	74	86.1
Total	86	
Total number of cases of urinary calculi in Sabah Hospital in the same period	1752	

Table II
Location of the Urethral Calculus

	No. of Cases	Percentage
Posterior urethra	32	37
Anterior urethra	45	52.5
External meatus	9	10.5
Total	86	

Table III
Associated Other Urinary Calculi

	No. of Cases	Percentage
None	58	67.4
Vesical	9	32.6
Ureteric	4	
Renal	8	
Multiple bilateral	7	
Total	86	

We advise against the use of stiff or metal catheters to relieve acute retention if a soft catheter fails to pass. It is better in such cases to use a medium-sized sound, only as a gentle diagnostic tool to differentiate between urethral stricture and stone. Once a calculus is detected, its depth should be measured and the sound withdrawn. Sometimes when the obstruction is partial, with dysuria and frequency, the case will have to be differentiated from acute cystitis.

Table IV
Associated Lesions of the Urinary Tract

	No. of Cases
Normal U.T. otherwise	39
Hypospadias	3
Meatal stenosis	2
Old rupture urethra and/or bladder	11
Bilharziasis complications	25
Prostatic lesions	5
Cancer of bladder	1
Total	86

Table V
Procedures performed

	No. of Cases
Spontaneous passage after sedation	6
External meatotomy	9
External urethrotomy (primary)	14
External urethrotomy (secondary)	3
Johanson Technique	9
Floating-in followed by lithotripsy	16
Floating-in followed by suprapubic operation	3
Suprapubic operation	8
Refused treatment after catheterisation	3
Ill-advised forceps extraction	15
Total	86

During X-ray examination the plain control film should include the whole of the urethral area, otherwise some urethral calculi will be overlooked. There were no radiolucent stones in this series.

Management of Acute Retention

The majority of cases present with acute retention either in the Casualty or the Emergency Reception Department.

From our experience we advise relief by suprapubic needle aspiration. This will allay the pain and anxiety present and will give time for a well-planned investigation and treatment under general anaesthesia. Also by avoiding repeated attempts at catheterisation there will be less urethral oedema and sphincteric spasm. It is interesting to notice that this policy has been rewarded by spontaneous passage of the stone in 6 of our cases (Table V).

Treatment (Table V)

It should be stressed that forward massage of the urethra, in an attempt to "milk" the stone out, is inadvisable, as the delicate urethral epithelium will be irreparably damaged.



Fig. 1. A shell-like stone in the bladder, with a similar fragment in the posterior urethra. History of a long-standing indwelling Foley catheter, around which the stone had apparently formed.



a



b

Fig. 2a, b. Large dumb-bell shaped urethro-vesical stone. The constriction was at the level of the bladder neck.



Fig. 3. A smaller dumb-bell-shaped urethral stone. The constriction was at the level of the external sphincter.

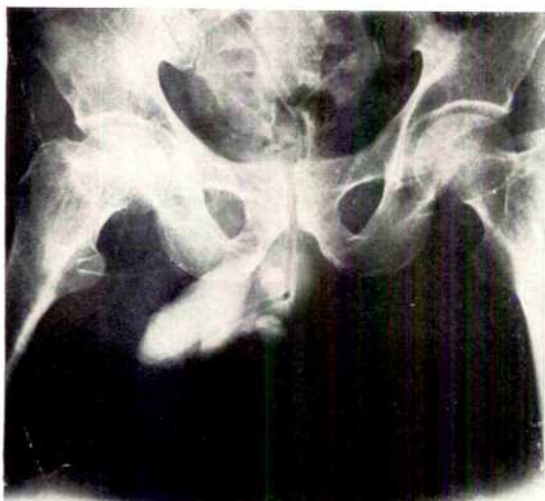


Fig. 4. Multiple urethral calculi which presented as perineal infection and multiple urinary fistulae.



Fig. 5. Large calculus in a urethral pouch, which presented as a perineal tumour.

Attempts at extracting or crushing the calculus using forceps is an operation to be condemned, because of the damage that can occur to both the urethral mucosa and the periurethral tissues. The only circumstance in which this may be acceptable is when the stone is at the external meatus. But even in this situation an external meatotomy will be a less traumatising procedure.

1. **Meatotomy.** This is advised if the stone is impacted at the external urethral orifice, or in the fossa navicularis.

2. **External Urethrotomy.** This is the method of choice for a calculus present in the penile urethra. After removing the stone the incision is closed in 2 layers, without tension. We did not find any necessity for urinary diversion, or an indwelling urethral catheter. There should be no fear of inadequate healing or the development of a fistula, provided that the operation has been performed as a primary procedure, with no traumatising attempts at extracting the stone.

3. **Johanson Technique.** This is advised for stones in the anterior urethra in cases previously traumatised by unsuccessful attempts at extraction and also in cases of stone impacted behind a stricture. After formal external urethrotomy the mucosal edges of the urethra are sutured to the skin as in the first stage of Johanson urethroplasty, and this may be combined with excision of any damaged and infected tissues. At a second stage a few weeks later the urethra is closed again.

4. **Irrigation or Retrograde Manipulation of the Calculus into the Bladder.** This is the best procedure for stones in the prostatomembranous as well as the bulbous urethra. Under general anaesthesia the external sphincter should not prevent dislodging of a stone from these sites backwards into the bladder. Though a bougie would appear to be the suitable instrument to dislodge the impacted calculus, its use is not always desirable as there is a definite danger of traumatising the urethra at the site of impaction. It is better to attempt to irrigate the urethra to disimpact the stone and return it to the bladder, after which litholapaxy or suprapubic removal can be performed. This method has been used in 19 cases in the series with complete success and without complication. A plastic catheter is inserted into the urethra, and the urethral lumen around it is occluded by digital pressure. Saline irrigation of the catheter will cause the majority of calculi to pass backwards into the bladder. If an aqueous solution is unsuccessful, then an oily substance such as liquid paraffin can be utilised with success. Obviously this manoeuvre is not applicable to long-standing dumb-bell-shaped calculi such as those shown in Figures 2 and 3. In these cases suprapubic exposure combined with rectal digital manipulation are necessary to dislodge the stone.

5. **Perineal Urethral Diverticulectomy.** This procedure is required in the rare event of the calculi being lodged in pouches or diverticula of the urethra.

Management of Associated Lesions

Priority is given to the relief of acute retention and removal of the urethral stone. But consideration should be given to associated lesions such as vesical calculi, diverticula or prostatic hypertrophy which can be treated under the same general anaesthetic.

Postoperative Surveillance

(a) Even when the urethral stone is the only manifestation of urolithiasis, a full urological and metabolic investigation is advised.

(b) Urethrography and urethroscopy are advisable 3 to 4 weeks later to exclude pre-existing pathology in the urethra (*e.g.* stricture or pouch). Debenham (1930) stresses the importance of

the unhealthy urethra as a predisposing cause for the local development of primary stones or the impaction of migratory ones descending from the bladder.

(c) It is felt that local applications to the urethra of hydrocortisone and nitrofurantoin in urethral suppository form may help to diminish the incidence of later stricture formation. This is especially important in traumatised cases.

Discussion

The apparent ease with which urethral stones can be crushed or extracted is very tempting, but usually leads to unnecessary urethral trauma.

In many textbooks of surgery there is little mention of the management of urethral calculi. Considering the fact that such acutely presenting cases are more liable to unspecialised management, it is felt that a standardised safe policy of treatment should be detailed. Winsbury-White (1948) and Bailey (1962) advised external urethrotomy for anterior urethral stones only as a last resort following failure of repeated manipulations. These included the following techniques:

- (a) The use of forceps to extract or to crush the stone.
- (b) The use of bent probes to rake the stone down.
- (c) Downward "milking" of the stone.
- (d) Passage of multiple filiform bougies beyond the stone, followed by application of traction.

To this list of manoeuvres Debenham (1930) adds the use of a curette spoon and Fitzpatrick (1957) suggests the application of a wire stone basket. It is felt that these manipulations are too traumatising for the urethra, and are inadvisable. The fact that the patient can be discharged on the same day (Debenham, 1930) cannot be accepted as an advantage. Straffon and Higgins (1970) discouraged external urethrotomy because of the danger of fistula formation; but this complication did not occur in any of our 14 cases in which external urethrotomy was performed as a primary procedure (Table V). Only when it was carried out as a secondary procedure after the failure of traumatising attempts at extraction did we notice breakdown of the suture lines with resulting fistula formation. We feel that in such cases a first-stage Johanson urethroplasty may be preferable to simple external urethrotomy.

Suprapubic puncture by simple aspiration relieves acute retention and allows time for better arrangements for diagnosis and treatment (Cameron, 1963; Tinckler, 1967). It also adds to the safety of management of urethral calculi, because it avoids the oedema and spasm which may result from repeated attempts at catheterisation.

Few reports have been made of long-standing large urethral calculi such as those reported in this series. The rarity of such cases has also been noted in other areas where urolithiasis is as frequent as in Kuwait (Vanderhorst, 1958).

Summary

86 cases of urethral stones are presented. The clinical picture, diagnosis and management are discussed in detail. Emphasis is laid on the following 4 points, which are felt to have special importance in diagnosis and management:

- (i) Diagnostic failure on account of the use of X-ray films short of urethra.
- (ii) Advisability of suprapubic vesical puncture for acute retention, to allow time for better management of the stone.
- (iii) The use of urethral irrigation by saline or paraffin to dislodge stones impacted in the bulbous or posterior urethra backwards into the bladder.
- (iv) The use of external urethrotomy as a primary procedure for calculi in the anterior urethra.

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Urethral Valves¹

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The primary lesion of posterior urethral valves is a simple one which might be expected to respond readily to simple transurethral resection. Nevertheless, the total care of a boy with urethral valves can be a most complicated undertaking. The object of this paper is to describe a new method of valve ablation and to identify and discuss the factors leading to failure of recovery and to persistent urinary infection.

Patients

From 1951 up to October 1972, 206 boys with posterior urethral valves have been treated by the senior author; of these, 172 presenting before the end of 1970 are available for statistical analysis.

Clinical Features

Presentation

Table I shows the age distribution indicating that just over half the boys presented under 1 year of age, one-third of them being under 3 months. The mean age of all cases was $2\frac{1}{2}$ years. Table II shows how the symptomatology varies with the age of presentation: most children have a combination of the symptoms and signs listed. In the older boys infection and incontinence were common; the younger children had more frequently general signs of renal failure. At all ages infection was important and at times seemed to have had a value in drawing the attention of the doctor to the presence of a serious lesion of the urinary tract which might otherwise have escaped notice for some years.

Certain misleading presentations may be remarked upon: a number of children had abdominal enlargement apparently due to intestinal distension; in these there was a great deal of oedema on the posterior abdominal wall around infected dilated ureters. Some children had a remarkably good urinary stream, and in them it appeared that massive hypertrophy of the bladder was able to compensate for the obstruction at the expense of very considerable upper tract damage, so that paradoxically some of the children with a good stream had the most serious renal destruction. At other times renal enlargement rather than bladder distension was the prominent feature, and with infection there was sometimes a pyonephrosis.

Diagnosis

The diagnosis was made in almost all cases by the findings in intravenous pyelography and micturition or expression cysto-urethrography. Any difficulties which arose were in older enuretic children with doubtfully obstructive valves in the posterior urethra, but such cases have been excluded from this series. We are here concerned with unquestionable obstruction. Thus, of 144 boys who survived there were 124 whose pre-operative pyelograms were available for assessment and of these only 22 had normal upper urinary tracts. The remainder had varying degrees of

¹This paper formed the basis for the Robert V. Day Lecture delivered by D. Innes Williams to the Western Section of the American Urological Association in Vancouver, 1972.

Table I

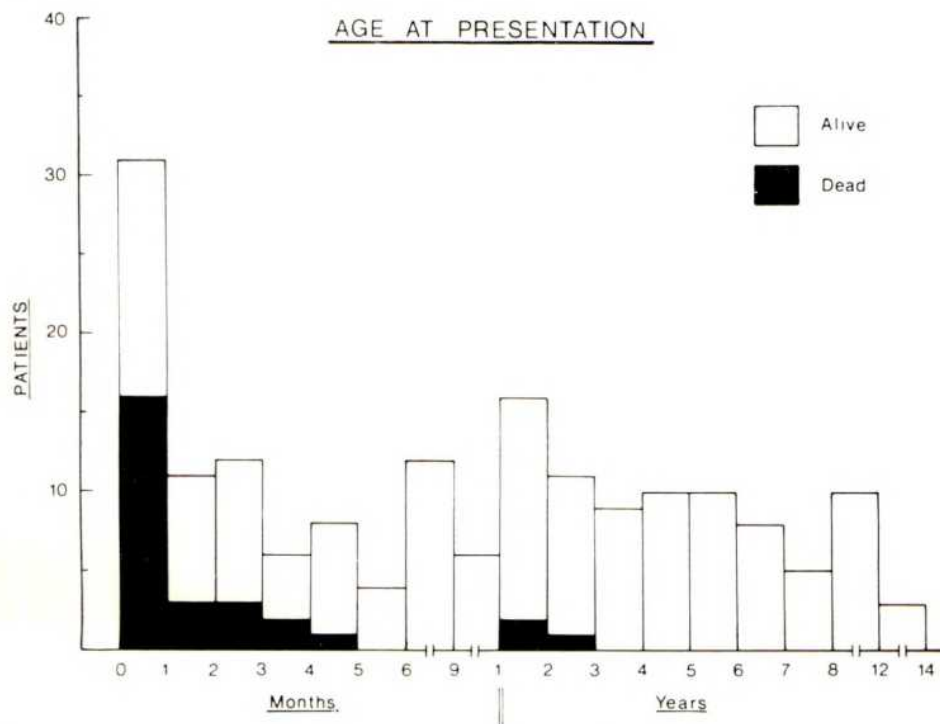


Table II

Symptoms and Signs	< 3m %	3m-1y %	1y-5y %	> 5y %	All %
Distended bladder	62	62	64	43	56
Poor stream or difficulty	12	15	23	32	20
Failure to thrive or vomiting	35	44	50	5	29
Urinary infection	18	24	41	39	29
Haematuria	8	6	14	2	6
Incontinence or dribbling	20	24	23	48	30
Acute retention	7	3	5	7	6
Other	12	6	0	7	9
Numbers	54	36	26	56	172

dilatation, and in 31 one or both kidneys failed to opacify on the initial urogram. In the earlier years an intravenous pyelogram was not performed as a routine on uraemic cases so that the figures given minimise the number of cases with upper tract dilatation.

Management of the Infant Emergency

The uraemic infant constitutes the most difficult problem in the management of urethral valves. The mean blood urea of all cases on admission was 102 mg per cent, but a number of the older children had a normal upper urinary tract, uraemia being largely a feature of the neonates.

The initial examination demands a clinical assessment of the general condition, particularly the state of hydration and the degree of distension of the bladder or kidneys. Immediate urinary microscopy to detect the presence of pyuria is required pending the results of urine culture studies. Estimation of blood urea, electrolytes and haemoglobin are obviously essential, but studies of blood gases, of plasma pH, of serum calcium and magnesium have also proved of value recently. Intravenous pyelography is carried out routinely when the blood urea is high, but no attempt should be made to dehydrate an infant in these circumstances.

The programme of medical management, emergency drainage and definitive surgery must be carefully integrated, since the chances of survival from any operation are greatly enhanced if the biochemical state is first corrected. Our present routine is as follows:

If the child's condition on admission is good, the blood urea less than 100 mg per cent and hydration adequate, early ablation of the valves is planned. If the bladder is very tense it is drained by an indwelling urethral catheter in the meantime.

If the child's condition is poor, management depends upon an estimate of the capacity for improvement under medical treatment and the sterility or otherwise of the urine.

Sterile Cases. A dehydrated baby with acidosis but with sterile urine can be treated by catheterisation and re-hydration. Where, however, the blood urea remains high despite drainage, re-hydration and a low protein milk diet, it is clear that severe renal damage is present and that upper urinary tract drainage is likely to be required. A child whose condition is poor, who is already over-hydrated or has severe electrolyte disturbance but sterile urine, may best be treated by peritoneal dialysis.

Infected Cases. In any child the presence of a urinary infection will influence us in favour of early operative intervention, but immediate antibiotic therapy is instituted, usually with gentamicin, pending the results of urine culture and sensitivity tests. A severe infection with renal enlargement is best treated by emergency nephrostomies.

In the earlier part of the series *pre-operative catheterisation* was used as little as possible, but with the manufacture of better plastic catheters drainage by this route is safer and can be employed for a few days. We now ordinarily use an 8 F polythene infant feeding tube.

Bilateral nephrostomy has been performed with a 14 F malecot catheter: it is a simple operation and efficient for short periods, but long-term nephrostomy has been little used as we have encountered troubles with infection around the tube and great difficulty in replacing a tube which fell out prematurely. Temporary diversion was performed in 74 out of the 172 cases, and of these bilateral nephrostomy was the method employed in 38. *Ureterostomy-in-situ* had been used in some cases referred to us, but it did not appear to be a very satisfactory form of drainage because of the tortuous nature of the ureter. *Cutaneous ureterostomy* has been employed in a number of boys and the results are discussed below.

Operation for Urethral Valve Ablation

In the series analysed the valves were approached suprapubically in 5, and endoscopically in the remainder. In 92 boys in the younger age group, perineal urethrostomy was essential although it will become less so with the development of better instruments. In approximately a quarter of the cases the valves were destroyed with a simple diathermy electrode; in the remainder a resectoscope

loop was employed. In 11 per cent a second operative procedure was necessary, reflecting our reluctance to perform a deep resection because of the danger of subsequent incontinence.

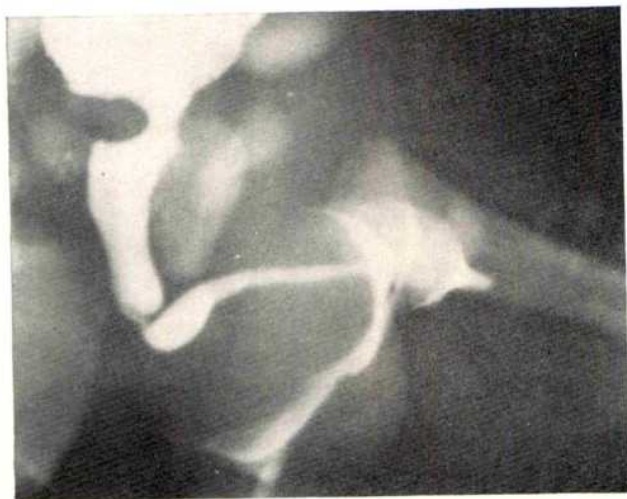


Fig. 1. Micturating cystogram in a 3-month-old boy showing urethral obstruction due to valve with clearly defined anterior curtain-like membrane.

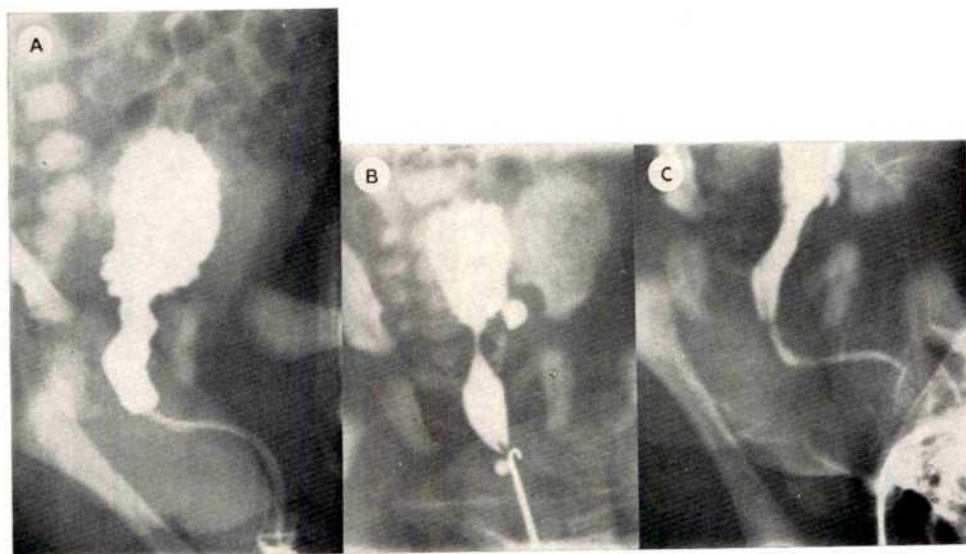


Fig. 2. Cystography and urethral valve ablation with diathermy hook. **A,** Shows expression cysto-urethrogram with clear cut valvular obstruction. **B,** Shows the diathermy hook engaged in the valve prior to ablation. **C,** Expression cystogram immediately after ablation showing free passage of opaque medium into anterior urethra.

During the past year experiments have been made with other forms of valve ablation. Any form of endoscopic treatment requires the introduction of a relatively large instrument to carry the light and the telescope, but the obstructive valve is much more easily seen by radiological screening. This consistently shows that the important element of the valve is the membrane attached anteriorly to the urethral wall (Fig. 1), whereas endoscopy allows easier visualisation of the ridges which constitute the margin of the opening in the valve posteriorly. Endoscopic resection is therefore apt to cut the postero-lateral ridges rather than the more obstructive anterior membrane.

It was perhaps the practice of demonstrating valves at post-mortem by splitting the urethra longitudinally through an anterior midline incision, which led to the belief emphasised in Young's classification that there are two lateral valves rather than an anterior curtain with a posterior opening.

In the endeavour to avoid the introduction of an endoscope in a neonatal case a trial was made of rupturing the valve by the sharp withdrawal of a Fogarty catheter under X-ray control: this was effective in 3 very young infants, but more recently ablation of the valve has been achieved by the introduction of an insulated diathermy hook, as shown in Figure 2. Under radiological control the hook is pressed against the ventral wall of the posterior urethra and drawn downwards until it engages in the valve. This engagement can be felt as well as seen on the television screen. By applying the diathermy cutting current while the valve is engaged the obstructing membrane is ruptured and the completeness of relief of obstruction can be immediately verified by the freedom with which the opaque medium passes into the anterior urethra. This method entirely avoids the necessity for a perineal opening in neonates with corresponding lessening of the infection problem. A urethral catheter has been left in for 2 days only and its withdrawal has been followed by normal micturition in the 3 cases on which it has been employed.¹

42 boys (24 per cent) had a procedure to widen the bladder neck by Y-V plasty or endoscopic resection: it was felt in earlier years that a secondary bladder neck obstruction might complicate urethral valves, but recently we have found little evidence of obstruction at this level and since there is a high risk of incontinence following bladder neck revision (Whitaker *et al.*, 1972) our inclination has been to avoid surgery at this level.

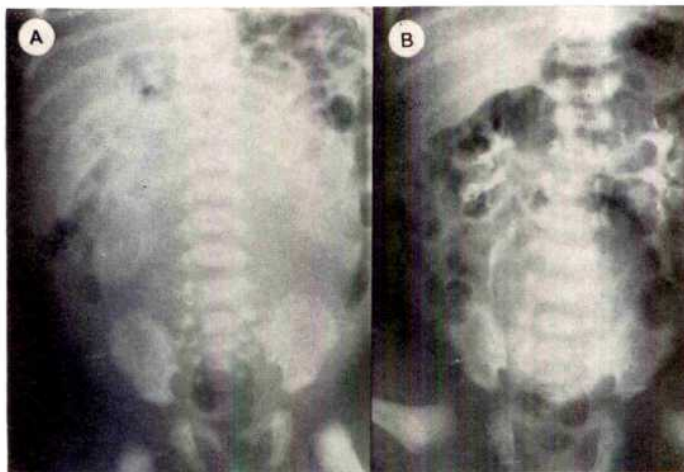


Fig. 3. Intravenous pyelography 2 days before and 3 days after urethral valve ablation. A, Shows bilateral hydronephrosis. B, Shows return to normal calyceal pattern.

Early Post-operative Management

In the series as a whole postoperative infections have been common and there has been a number of biochemical disturbances, some of them serious. In infants with a very acute type of obstruction, often evidenced by a nephrogram in the pre-operative I.V.P., there has been a tendency to diuresis with sodium loss, but these children have ultimately a good prognosis and often the first post-

¹A total of 7 neonatal cases have now been treated by the diathermy hook: in all the obstruction has been satisfactorily removed but 1 required perineal urethrostomy drainage for 5 days because of a slight extravasation from the bulb of the urethra.

operative I.V.P. shows an amazing improvement (Fig. 3). Other cases with less acute obstruction may have less easily reversible changes in the urinary passages and more long-lasting disturbance of renal function. Sometimes these problems have been readily controlled by antibiotics, parenteral fluids and a low protein diet, but sometimes persistent infection and failure to improve renal function have necessitated further surgery.

Management of the Upper Urinary Tract

The Functionless Kidney

If the kidney on one side has ceased to function there is obviously little point in preserving it, particularly as it may well be the major focus of infection. In all, 24 out of 172 boys had a kidney removed. In 15 of these the pre-operative pyelograms showed no opacification. There was gross hydronephrosis in 6, but reflux may have been responsible for outlining some of these kidneys. The failure of function was usually demonstrated by cutaneous ureterostomy. It is remarkable that the upper tract damage in urethral valve cases is usually asymmetrical, one side being much more severely damaged than the other, and while unilateral reflux may often be the factor involved it did not appear to be so in all.

Reflux

Overall, reflux was present in 44 per cent of children in whom adequate pre-operative data were available for review. In 16 per cent it was bilateral, in 28 per cent unilateral. It ceased spontaneously after valve resection in 17 out of the 63 children analysed, and the fate of the remainder is set out in Table III.

Reflux may occur with or without a para-ureteric sacculi: when a sacculi is present there may be an element of obstruction to downflow as well as reflux backflow (Fig. 4).

Fig. 4. Micturating cystogram showing bilateral para-ureteric sacculi with normally emptying bladder after urethral valve ablation.

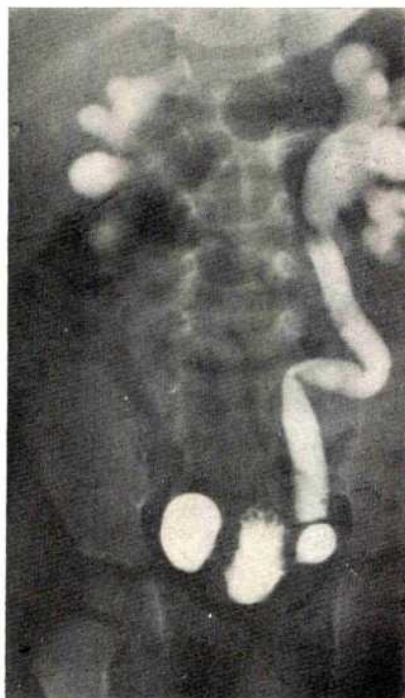


Table III

Vesico-ureteric Reflux

63 boys had pre-operative reflux (44 per cent)
A total of 86 pre-operative refluxing ureters
were analysed as follows:

Stopped spontaneously	22
Cured by surgery	12
Dried	8
Permanent diversion	2
Persistent reflux (no surgery)	20
No postoperative M.C.U.	13
Primary nephrectomy	9
	—
	86

11 ureters previously non-refluxing developed
reflux postoperatively

In reviewing the figures we have been surprised to find that reflux is not such a serious complication of urethral valves as had been anticipated, and the difference between the children with and without reflux was not so remarkable. The mortality was, in fact, lower in the refluxing group (9.5 per cent against 12.5 per cent), but the pre-operative infection rate was somewhat higher (56 per cent against 45 per cent). The incidence of nephrectomy for functionless kidney was also higher when there was reflux; in the nephrectomy cases reflux was present in 61 per cent of children, whereas the overall incidence of reflux was 44 per cent. Judged by the blood urea levels the renal function did not differ significantly in the two groups.

Persistent Ureteric Dilatation without Reflux

Dilatation of the ureter persisting after restoration of bladder function can be due to a failure of ureteric peristalsis or to the presence of a uretero-vesical obstruction. There is a further possibility that the extremely hypertrophied bladder present in these cases may, even after relief of obstruction, retain normal volumes of urine at abnormally high pressures and thus prevent free drainage from the ureters. The differentiation of these various factors is at present being studied by pressure/flow measurements, as described by Whitaker (1973), and a later paper will give details of the results.

In the retrospective series the distinction between an intrinsic ureteric failure and a ureteric obstruction was not clearly made, but the figures available emphasise the fact that it is not simply reflux which causes persistent upper tract disturbance. Thus, of non-refluxing ureters pre-operatively 67 per cent showed gross dilatation or non-function; post-operatively 48.5 per cent had still to be put in this category. In the earlier part of the series an expectant attitude was always adopted towards such persistent dilatation, and in many instances this was rewarded by slow but steady improvement in the radiological appearance of the ureters together with improvement of renal function. It is clear that provided the urine can be maintained free from infection such an expectant attitude is justifiable. In a small number of cases the ureter became more dilated in the postoperative period and in these the involvement of the lower end of the ureter with a para-ureteric sacculus was the usual finding, more often with obstruction than with reflux.

Operations on the Ureter

In a total of 25 boys, *cutaneous ureterostomy* was performed on the hypothesis that such free drainage would allow control of infection, improvement of renal function and recovery of ureteric peristalsis with some reduction in calibre. The operations were initially performed in the expectation that this recovery would allow restitution of the ureter at a later stage, perhaps after some months. In 8 boys, however, permanent diversion was necessary because of chronic renal failure and persistent infection, often with the additional problem of incontinence. One of the kidneys was found to be functionless in 10 cases and nephrectomy was performed on that side.

Loop Ureterostomy. Most of the ureterostomies were performed by the loop method, in which a length of ureter is brought to the surface and opened laterally, but not cut across. The abdominal muscles, and sometimes the skin, were brought together behind the loop. This proved in most cases to be a simple procedure, although in some there was difficulty in preventing obstruction from kinking of the ureters, and in others there was bleeding from the cut edge of the ureter in the postoperative phase.

Terminal Ureterostomy. A smaller number of cases had terminal ureterostomies, the ureter being divided at the bladder level and brought directly on to the surface. This procedure was undertaken in refluxing cases with the idea that re-implantation at a later stage would both close the ureterostomy and prevent reflux at a single procedure.

Restoration of Continuity in Cutaneous Ureterostomy. The results of these procedures were reported by Lome and Williams (1972); 16 bilateral *loop* cutaneous ureterostomies were analysed in valve cases, 24 ureters being reconstructed by excision of the exteriorised portion and anastomosis of the ends. Four ureters developed complications secondary to closure of the loop, which ultimately responded to a second operation. The effects of some months of external drainage in these cases was some improvement in renal function, some diminution in calibre and slight restoration of peristaltic activity. The general health of the child improved considerably, but the local effect was perhaps less than had been hoped. Restoration of continuity gave satisfactory function if reflux was absent, but was followed by deterioration if reflux was present. In later cases a reflux prevention operation of the Gregoir type was performed at the same time as closure of the loop.

Terminal ureterostomy was less satisfactory in that drainage from the cutaneous stoma was not so reliable, perhaps due to kinking of the long length of ureter above, perhaps due to greater tendency to stenosis of a terminal stoma; and after restoration of continuity by re-implantation of the ureter into the bladder several late stenoses occurred.

Lome, Howat and Williams (1972) also analysed the effects of defunctioning the bladder by cutaneous ureterostomy: in 21 defunctioned bladders in association with urethral valves 6 became seriously contracted. They were mostly cases who had had considerable inflammation of the bladder wall; 3 of them required permanent diversion, but 3 subsequently enlarged after restoration of the ureteric continuity on one side.

With a view to obtaining the benefits of free drainage by cutaneous ureterostomy without completely defunctioning the bladder the *Y type of ureterostomy* suggested by Sober (1972) was employed in a few cases, many of them after the close of the analysed series. While this system has given good results in older children with grossly dilated ureters, in the uraemic neonate the cutaneous limb of the Y, which has a terminal stoma on the skin, has tended to stenose and retract so that free drainage was not obtained.

Although it is difficult to substantiate from a statistical analysis we have the impression that loop ureterostomy was of considerable value in a number of uraemic infected children and that by this method their kidneys were preserved.

There is no doubt that in some cases ureterostomy was performed unnecessarily and improvement could have been seen with simpler methods, but a place remains for ureterostomy drainage in the infected case with renal failure.

Remodelling and Re-implantation of the Ureter into the Bladder. The alternative operative approach to the persistently dilated ureter has been re-modelling and re-implantation into the bladder. Although because of the diversity of the material and varying methods of treatment the series analysed does not give any useful numerical assessment of the value of this procedure, re-implantation has been strikingly successful in clear-cut cases of obstruction due to involvement in a sacculi (Fig 5); re-implantation with re-modelling has also been of value in children over the age of a year with a chronically dilated ureter which was incapable of obliterating its lumen and so of propelling the urine forwards.

In order to test the hypothesis that it was the ureteric failure rather than the obstruction which maintained the dilatation, re-modelling was performed on one side and re-modelling together with re-implantation on the other in 3 children. There did not appear to be any very important differences in the 2 sides at follow-up. Nevertheless it is usually hard to avoid the impression of a uretero-vesical obstruction in these cases and simple remodelling can seldom be justifiable. Even so, in several chronic cases there have been disappointing results from re-implantation and even some deterioration after operation; it is never easy to obtain a reflux-preventing but unobstructed junction between a grossly dilated ureter and a massively sacculated and trabeculated bladder.

We have not undertaken the immediate reconstruction of the urinary tract in neonatal cases as advised by Hendren (1971), but in the extensive re-modelling done in early infancy since the

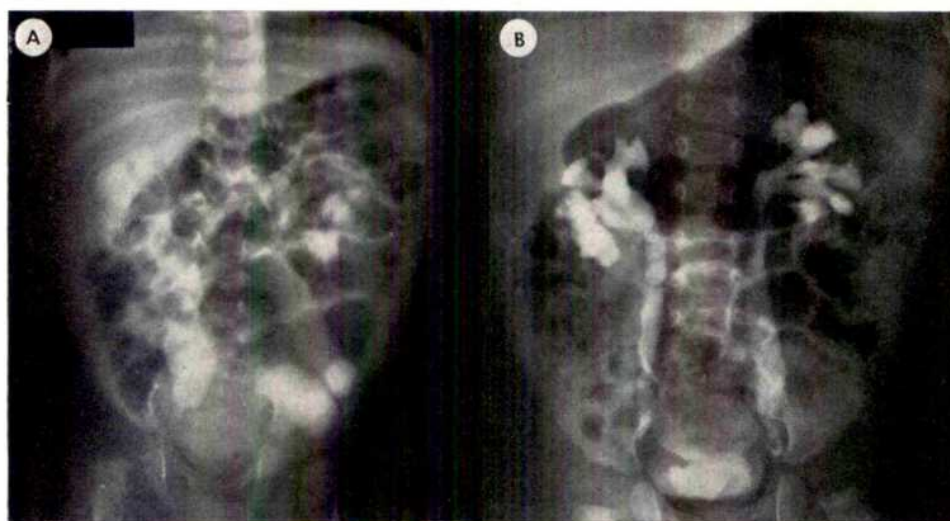
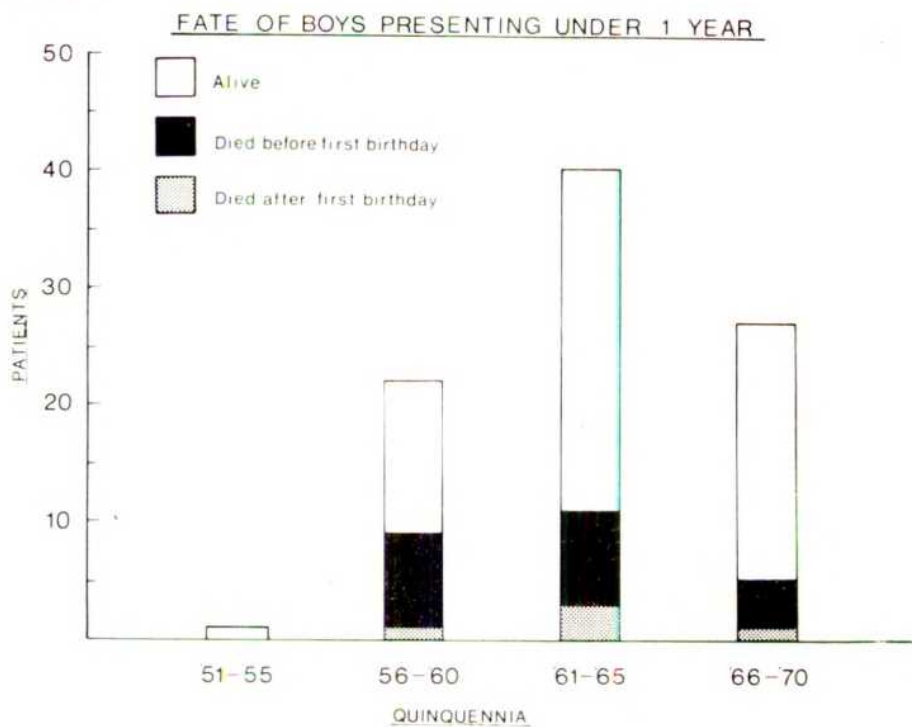


Fig. 5. Intravenous pyelogram before and after re-implantation of ureters. A, Intravenous pyelogram after valve ablation and restoration of fully emptying bladder accompanied by persistent non-refluxing dilatation of ureters. B, Intravenous pyelogram after re-implantation of ureters showing a degree of recovery.

Table IV



close of the statistically analysed series our results have been disappointing compared with the improvement obtained by cutaneous ureterostomy. Re-modelling can give a ureter of lesser calibre and perhaps with better function, but where the kidney substance has already been excavated by long-standing obstruction this excavation remains. Moreover, the appearances after re-modelling are somewhat misleading in that there may be an obstruction at the lower end of a ureter which appears to be of more or less normal calibre. From our own experience and from cases referred to us from other centres we believe that there are considerable hazards to extensive re-modelling and re-implantation in the neonatal period.

Mortality

28 out of 172 boys (16.2 per cent) died. All but 3 of the 28 presented under the age of 1 year, and it is clear that a very early presentation is unfavourable. Of the 54 children presenting under the age of 3 months 22 (40.6 per cent) died. In retrospect it is not possible to be certain of the cause of death, but amongst the causes quoted in autopsy reports were: renal infarct, subdural and cerebral haemorrhage, peritonitis, urinary ascites, pyonephrosis, peri-nephric abscess, perforated duodenal ulcer, patent ductus arteriosus and dysplastic kidneys. There is evidence that the 28 boys who died were the more seriously ill at the time of admission: their mean blood urea was 155 mg per 100 ml as opposed to 92 mg per 100 ml for survivors. Nevertheless, over the years the mortality has fallen, and while it is clear that a few babies will be born with inadequate renal tissue for survival, the proper medical and surgical management should carry the great majority through, at least into adolescence. Thus, from 1956 to 1960, 36 per cent of infants treated under the age of 1 year were dead before their first birthday. In the period 1961-65 the corresponding figure was 20 per cent and in 1966-70 it was 15 per cent (refer to Table IV). In the last 2½ years of the survey period, and since that time, there have been no deaths amongst 21 boys, 9 of whom presented under the age of a year. There have been no obvious changes in the referral pattern during this period.

Late Follow-up

The 144 boys who survived have been followed for a mean period of 5 years, 7 months; the longest period being 15 years. The mean age at the end of 1970 was 8 years, 6 months; the oldest patient was 25 years.

Features of the follow-up requiring comment are renal function, urinary infection and continence. With regard to *renal function* the mean blood urea level decreased postoperatively in surviving cases from 92 mg to 43 mg, per 100 ml whilst in the boys who died there was a mean blood urea on admission of 155 mg, which rose to higher figures prior to death. There was only 1 boy among 144 survivors whose postoperative blood urea level at 91 mg was higher than the pre-operative level of 60 mg. Nevertheless, in 17 survivors high blood urea levels remained. All had had extreme dilatation of the upper tract with unilateral functionless kidneys in 5; it would seem likely that there will be some increase in the late mortality of this group when the follow-up is carried further.

Information regarding *urinary tract infection* was available for pre-operative and postoperative periods in 102 boys; 50 had no infection before or after surgery; 28 of these had pre-operative infections but were sterile afterwards. "Persistent" infection was defined as more than 1 attack of urinary infection more than 1 year after surgery: 26, who had had infection before surgery, had persistent infection afterwards. All the boys who died had persistent urinary infection.

Postoperative incontinence in this group has been analysed in a previous paper (Whitaker *et al.*, 1972). Overall results show that of 112 patients, 33 were fully continent, 42 had some stress incontinence and 37 were continuously wet. However, careful investigation of this group showed that the young infants were much more liable to incontinence than were children treated in later

years, and that there was a definite trend toward spontaneous improvement, particularly about the time of puberty. Since the conclusion of this review the increased use of imipramine in incontinent patients has led to a surprising improvement in the situation. This presumably indicates that we are dealing not only with a simple sphincter weakness, but with some abnormality of bladder function as well. In a few cases implanted stimulators have been used with occasional success in some, but with disappointing results in more.

Summary

Our experience with 206 cases of posterior urethral valves in boys has been reviewed with statistical analysis of 172 cases followed up for at least 2 years.

A new method of valve ablation has been described.

The mortality in the disease has been confined almost to infants presenting in the first year of life with uraemia, and the results have improved enormously with better integration of medical and surgical corrective measures.

Later mortality is a comparatively uncommon event, but considerable morbidity occurs with recurrent infection, persistent dilatation of the ureter being the most important cause of this complication. Temporary diversion and re-implantation as alternative methods of treatment are discussed, but we have been impressed by the value of the conservative approach in many cases.

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Carcinoma of the Seminal Vesicle—with Particular Reference to the Angiographic Appearances

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The first case of primary carcinoma of the seminal vesicle was reported by Lyons in 1925. We here describe the 34th histologically documented case, the first report (to the best of our knowledge) to include the arteriographic features.

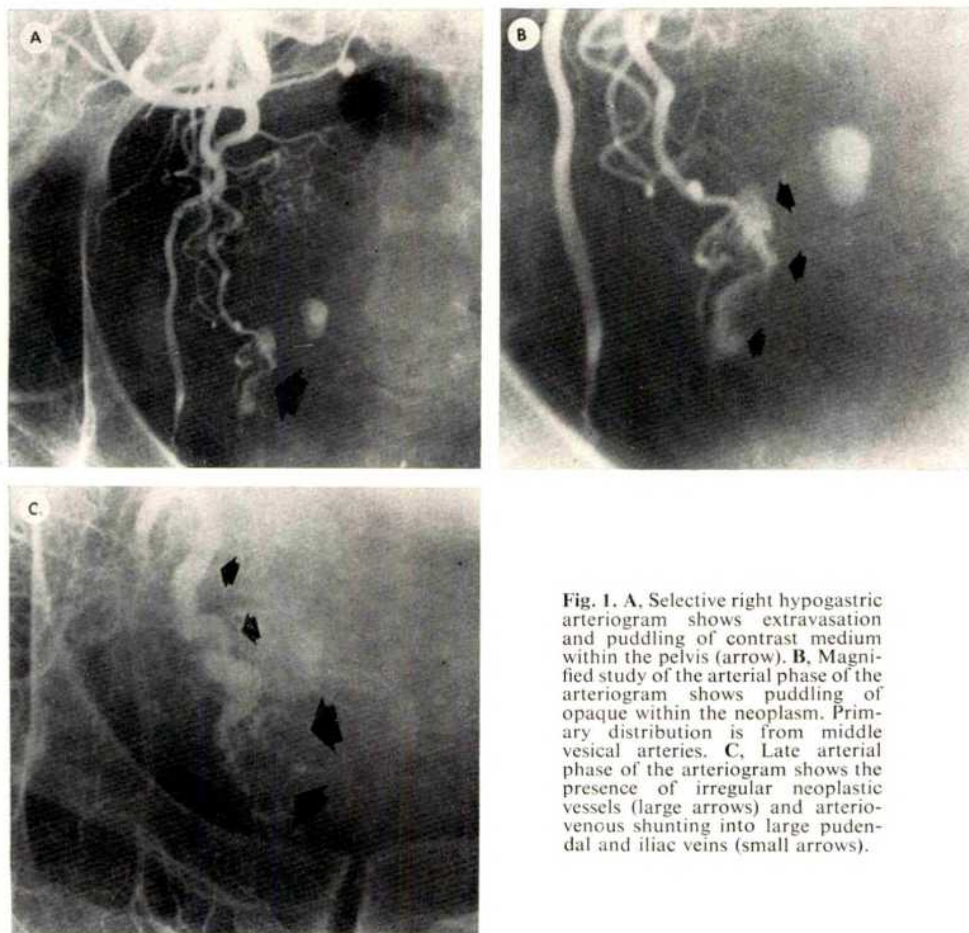


Fig. 1. A, Selective right hypogastric arteriogram shows extravasation and puddling of contrast medium within the pelvis (arrow). B, Magnified study of the arterial phase of the arteriogram shows puddling of opaque within the neoplasm. Primary distribution is from middle vesical arteries. C, Late arterial phase of the arteriogram shows the presence of irregular neoplastic vessels (large arrows) and arteriovenous shunting into large pudendal and iliac veins (small arrows).

Case Report

A 68-year-old white male gave a 5 weeks' history of dysuria, frequency, nocturia, right lower quadrant pain with radiation to the medial aspect of the right thigh. There was vomiting and weight loss, but no haematuria or obstructive urinary symptoms. On bimanual examination a firm nodular mass 6 cm in diameter was palpable just above the right superior aspect of the prostate, extending posterior to the bladder between the prostate and the rectum. It was discrete and freely movable within the pelvis. Intravenous pyelography was normal on the left side but there was delayed opacification on the right with dilatation down to the pelvic part of the ureter. Cystoscopy revealed a highly obstructive trilobar hyperplasia of the prostate. The verumontanum was unremarkable. The trigone was inflamed, oedematous and elevated especially on the right. A right retrograde uretero-pyelogram demonstrated hydronephrosis and irregular narrowing of the distal ureter. Transurethral biopsy and transperineal needle biopsy revealed only benign inflammatory changes. Pelvis arteriography demonstrated irregular neoplastic vessels arising from the superior and middle vesical branches with arterio-venous shunting. (Fig. 1)

At laparotomy a firm mass 8 × 4.5 cm was found arising from the right seminal vesicle. It was adherent to the anterior wall of the rectum. Although there was local peritoneal and iliac glandular involvement a radical cystectomy with uretero-ileostomy was carried out.

Histological examination showed an adeno-carcinoma with poor to moderate differentiation infiltrating the prostate, the bladder and the ureter. The patient died 3 weeks after operation. There was no autopsy.

Comment

Primary carcinoma of the seminal vesicle is seldom diagnosed pre-operatively. Diagnostic aids include intravenous pyelography, cystoscopy and biopsy, vesiculography and angiography. The last procedure has not previously been reported in primary carcinoma of the seminal vesicle. The appearances in this case were characteristic of a vascular malignant neoplasm but without obvious special features.

Summary

The angiographic findings in a case of primary adeno-carcinoma of the seminal vesicle have been presented.

The arteriographic features were those of vascular neoplasms in general; involvement of the middle vesical branches of the hypogastric artery may, however, suggest the diagnosis.

We wish to express our appreciation to Mr William Bow for his help in preparation of the photographs and to Mrs Delores Thomson for aid in preparation of the manuscript.

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A Malignant Sertoli Cell Tumour of the Testis

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Of 74 Sertoli cell tumours reported in the world literature, only 8 showed evidence of malignancy.

We are reporting the features of 1 additional case of a malignant Sertoli cell tumour.

Case Report

A Hindu male, aged 33 years, had a swelling of the right testis of 4 years' duration. Orchidectomy was done in a peripheral city hospital on 24th November 1969; the specimen was sent for histopathological examination to this laboratory. Eight months after the orchidectomy bilateral gynaecomastia appeared. About the same time the patient developed enlarged para-aortic and left supraclavicular lymph nodes. On 29th July 1970 a left supraclavicular lymph node was excised; this showed a metastatic deposit of cell tumour. The patient was then treated by radiotherapy. He was given a total dose of 2,150 rads from a cobalt-60 source to the para-aortic region and a total of 1,000 rads by DXR (240 kV) to the left supraclavicular lymph nodes. The patient is still alive 2½ years after the orchidectomy and 6½ years from the onset of symptoms. The bilateral gynaecomastia has persisted.

Pathology

Gross Findings. The specimen was of a right testis and spermatic cord. The testis was enlarged measuring $8 \times 7 \times 6.2$ cm; the spermatic cord was 2.6 cm in length. The cut surface of the testis was greyish white, opaque and lobulated in appearance. A few yellowish-brown areas of necrosis were also seen. At one pole a strip of compressed, residual testicular tissue was present. The spermatic cord appeared normal and not involved by the tumour (Fig. 1).

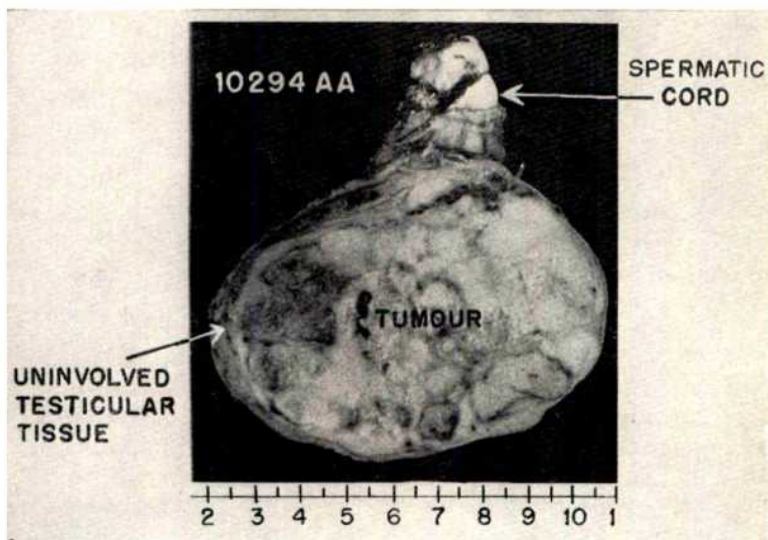


Fig. 1. Right testis.

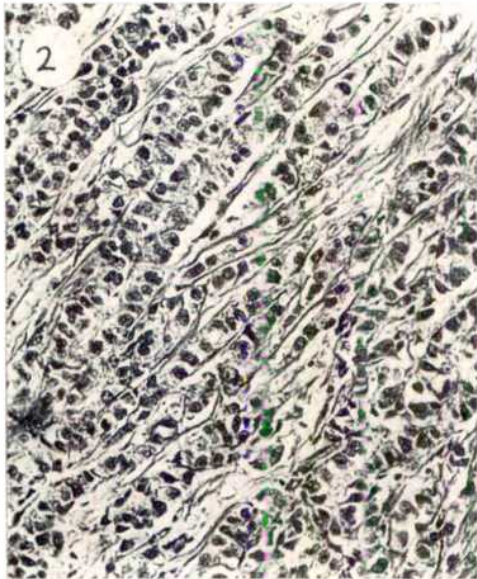


Fig. 2

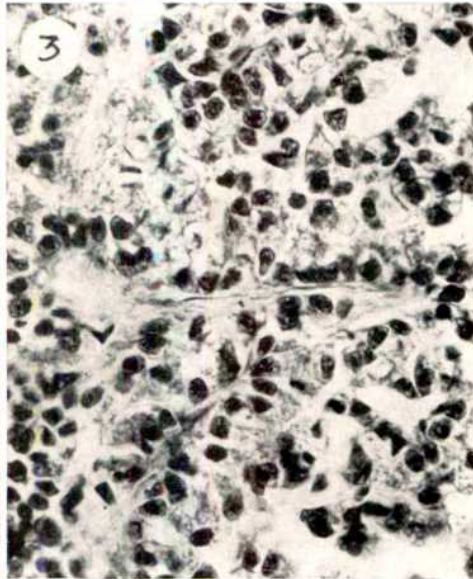


Fig. 3

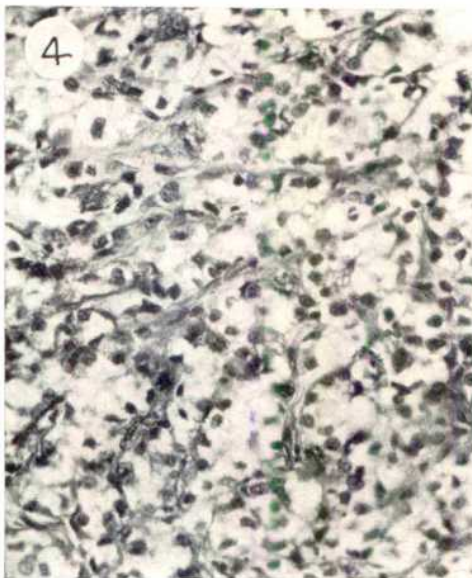


Fig. 4

Fig. 2. Photomicrograph showing all columnar cells with vacuolated or granular cytoplasm and round to ovoid hyperchromatic nuclei. The cells are arranged in tubules, with or without evidence of canalisation, surrounded by thin strands of connective tissue stroma. H & E stain $\times 140$.

Fig. 3. Photomicrograph showing cells in groups and columns with no attempt at canalisation and separated by connective tissue stroma. H & E stain $\times 280$.

Fig. 4. Photomicrograph of left supraclavicular lymph node showing metastatic deposit of Sertoli cells which resemble the cells in the testicular tumour. H & E stain $\times 150$.

Microscopical Findings. The tumour showed a tubular arrangement of the cells, except at places where they formed small groups or columns with no attempt at canalisation. The cells were tall, columnar with vacuolated or eosinophilic granular cytoplasm. The nuclei were round to ovoid and were hyperchromatic (Figs. 2 and 3). A few mitotic figures were also seen. Scanty connective tissue stroma was seen around the cells, while in some areas moderately dense collagenous tissue was present. Areas of necrosis were also seen. The uninvolved testicular tissue showed a few

Table
Summary of Data on 8 Cases of Malignant Sertoli Cell Tumours from the World Literature

Authors	Age in Years	Side	Clinical Features	Duration	Treatment	Size of Tumour	Metastases	Survival from Onset of Symptoms
Mostofi <i>et al.</i> (1959)	41	Left	Slow growing testicular swelling. Gynaecomastia 6 months	8 years	Orchidectomy	10.5 × 7.5 cm	Enlarged cervical lymph nodes and wide-spread metastases, 5 months after orchidectomy	Lived 8 years and 5 months
Collins and Symington (1964)	27	—	Hard, painless lump in testis. Gynaecomastia 5 months	1 year	Orchidectomy	Not mentioned	Clinical evidence of metastases	Dead. Lived 1 year and 3 months
Nagy <i>et al.</i> (1964)	35	Left	Testicular swelling	3 weeks	Orchidectomy	6 × 4 × 3 cm	Clinical evidence of metastases	Dead. Lived 1 year and 3 months
Nagy <i>et al.</i> (1964)	68	Right	Testicular swelling	1 year	Orchidectomy	Not mentioned	Enlarged abdominal lymph nodes 3 months after orchidectomy	Dead. Lived 1 year and 10 months
Rosvoll and Woodard (1968)	8	Left	Testicular swelling	3 years	Orchidectomy with bilateral retroperitoneal lymph-adenectomy. Radiotherapy and chemotherapy given	10 × 7 × 6 cm and attached 6 cm cystic mass	Enlarged retroperitoneal lymph nodes	Living for 5 years. No further follow-up
Hopkins and Parry (1969)	63	Right	Tender testicular swelling. Bilateral gynaecomastia, disappeared after orchidectomy	Incidental finding on examination	Orchidectomy. Prophylactic irradiation to para-aortic and iliac lymph nodes	8 × 4 × 5 cm	Bone metastases 3 years after orchidectomy. At autopsy extensive skeletal metastases and nodule in suprarenal gland	Dead. Lived 5 years
Talerman (1971)	79	Left	Testicular swelling gradually becoming painful. No gynaecomastia	6 months	Orchidectomy	7 × 5 × 4.5 cm	Enlarged right inguinal and right para-aortic lymph nodes 2 months after orchidectomy	Dead. Lived 9 months
Talerman (1971)	29	Right	Gradually increasing swelling of testis. No gynaecomastia	8 years	Orchidectomy. Radiation to abdominal and inguinal nodes	15 × 14 × 12 cm	Enlarged right lumbar lymph nodes immediately after orchidectomy	Living for 8 years and 8 months. No follow-up

isolated immature seminiferous tubules with no germinal cells. There were many dilated blood capillaries in the tunica albuginea.

Examination of the supraclavicular lymph node showed a metastasis (Fig. 4).

Comment

The tumour has been reported in the literature as androblastoma (Dixon and Moore, 1952), granulosa cell tumour (Scully, 1955), specialised gonadal stromal tumour (Mostofi *et al.*, 1959) and as Sertoli cell tumour (Collins and Symington, 1964).

Sertoli cell tumours of the testis commonly occur in dogs. In a study of 86 dogs with testicular tumours of all types Scully and Coffin (1952) reported Sertoli cell tumours in 28 of the dogs, 5 of these being bilateral. Metastases in lumbar lymph nodes were found in 2 of them. In autopsy findings Dow (1962) found 36 Sertoli cell tumours in 580 randomly selected dogs. Metastases were found in 5 of them.

Sertoli cell tumours are rare in men, comprising 0.6 per cent of testicular tumours (Collins and Pugh, 1964; Collins and Symington, 1964). As previously stated there are 74 cases of Sertoli cell tumours recorded in the literature, the largest number (23) being reported by Mostofi *et al.* (1959). Eight malignant Sertoli cell tumours have been reported to date, the present case being the ninth. It was the only Sertoli cell tumour in our series of 493 tumours of the testis.

The clinical features of the 8 cases are summarised in the Table.

Some Sertoli cell tumours are known to have a feminising effect, which is due to their producing oestrogen (Teilum, 1958). Mostofi *et al.* (1959) noticed gynaecomastia in 3 cases out of 23 Sertoli cell tumours studied by them. As shown in the Table, in 3 of the malignant tumours gynaecomastia was present; 1 of these had bilateral gynaecomastia, which disappeared after orchidectomy (Hopkins and Parry, 1969). In the present case bilateral gynaecomastia appeared 8 months after orchidectomy when the patient developed metastases, but the gynaecomastia persisted after apparently effective treatment of the metastases.

On naked eye examination benign Sertoli cell tumours are well demarcated from the residual testicular tissue, while the malignant growths are less well demarcated and often no normal testicular tissue is seen (Talerman, 1971). The present case showed compressed, uninvolved testicular tissue at one pole, which was well demarcated from the tumour, giving it a deceptively benign appearance.

Microscopic examination of malignant Sertoli cell tumours usually shows pleomorphism, multiple layers of Sertoli cells with tubule formation and numerous mitotic figures (Talerman, 1971). These features were not evident in the case reported here.

Summary

A case of a malignant Sertoli cell tumour (androblastoma) of the testis in a Hindu male aged 33 is reported.

A table summarises the features of 8 malignant Sertoli cell tumours of the testis previously recorded in the world literature.

In the present case the local appearances were deceptively benign and gynaecomastia persisted after apparently satisfactory control of tumour growth.

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Sarcoid of the Testis

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Sarcoidosis is a chronic granulomatous condition of unknown aetiology. Any organ in the body may be affected, but invasion of the genital tract is rare. Only 20 cases of genital sarcoidosis have been described in the literature and most of these were incidental findings at autopsy (Hines *et al.*, 1961). The usual treatment of testicular sarcoid has been orchidectomy (Krauss, 1958; McGowan and Smith, 1967). This is the first record of a case of sarcoid of the testis in which the testis has not been removed.

Case Report

A 24-year-old male with generalised sarcoidosis was admitted to the North Staffordshire Royal Infirmary in March 1970 because of breathlessness on exertion. The diagnosis had been made histologically in October 1967 when the patient presented with a swelling of the right lacrimal gland and eyelids. He had remained well till January 1970 when he was found to have widespread sarcoidosis.

A chest X-ray showed fairly severe pulmonary fibrosis with considerable enlargement of the hilar nodes. X-rays of his right hand showed skeletal involvement. There was granulomatous destruction of the basal phalanx of the third right finger and further involvement of the right thumb. Cutaneous sarcoid lesions were also present behind both ears.

While in hospital his left testis was found to be about one and a half times its normal size but not tender. The swelling did not transilluminate and was not fixed to the scrotal skin. The right testis and cord were normal.

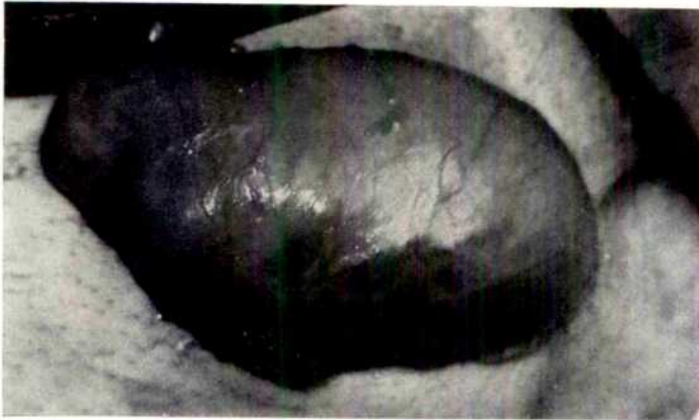


Fig. 1. Showing enlarged left testis delivered through groin incision.

Although the patient had widespread sarcoidosis, it was impossible to distinguish clinically between testicular sarcoid and a testicular neoplasm. In view of this difficulty, the left testis was explored through a groin incision on 12th March 1970. After temporary clamping of the spermatic cord, the left testis was delivered from the scrotum (Fig. 1) and a biopsy was taken. A frozen section was examined, and although the pathologist could not definitely say that it was sarcoidosis, he was certain that it was not a tumour. The testis was, therefore, returned to the scrotum and the inguinal incision closed. On paraffin section, the histological diagnosis was that of "a granulomatous orchitis typical of sarcoidosis" (Fig. 2).

The patient was given 10 mg prednisolone, 3 times daily postoperatively. When seen in the clinic 2 months later his general condition was improved. The groin incision was well healed and the left testis virtually normal to palpation. At a follow-up visit 21 months later, the testicle was indistinguishable from normal. The dose of prednisolone has been gradually reduced over this period. He is at present on 3 mg prednisolone daily.

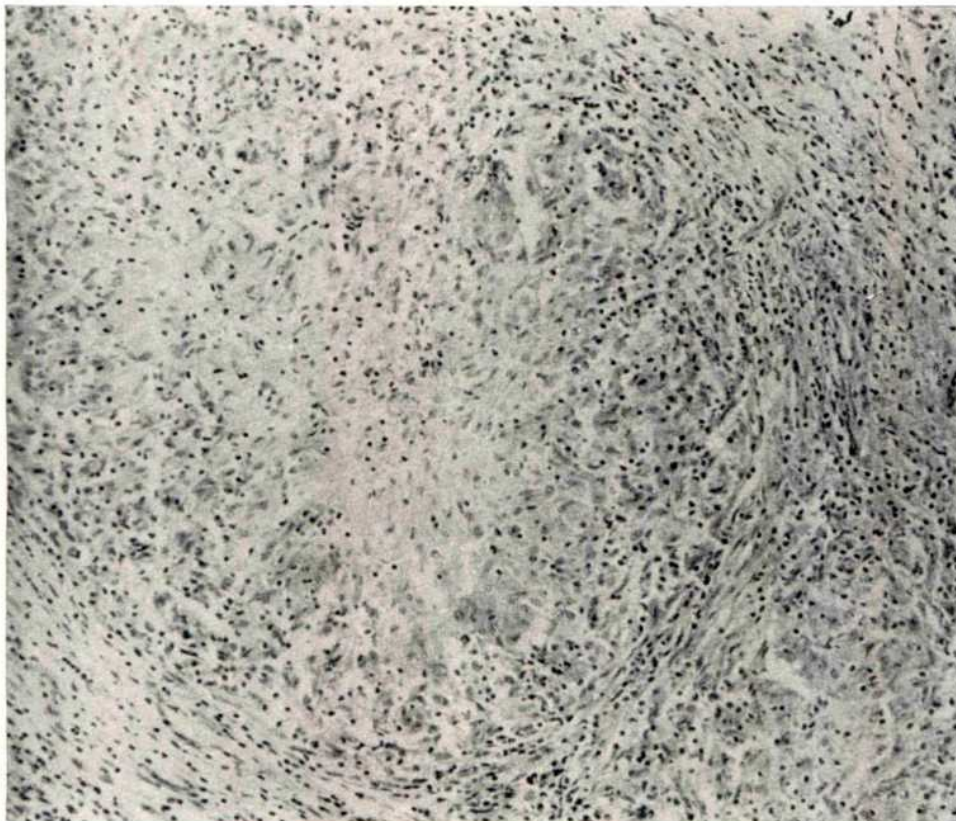


Fig. 2. Histology of haematoxylin and eosin left testis, showing a typical sarcoid follicle without caseation ($\times 180$).

Comment

Genital sarcoidosis is rare and the diagnosis cannot be made clinically with confidence as a testicular swelling due to sarcoidosis is indistinguishable from that due to a neoplasm. A biopsy of the exposed testis must therefore be carried out after temporary clamping of the spermatic cord.

The interpretation of the histological findings will not be easy. The typical granuloma of sarcoidosis with its epithelioid cells, giant cells and round cell infiltration closely resembles that found in granulomatous orchitis, and epithelioid granulomas may be so extensive in some seminomas (Spjut and Thorpe, 1956) as to give rise to a similar appearance. If this last possibility cannot be excluded with a reasonable degree of confidence by the pathologist, then clearly an orchidectomy must be performed. However, so long as the clinical and histological diagnosis of sarcoid of the testis can be accepted, the progress of the present case suggests that the testis can safely be replaced in the scrotum.

In view of the fact that in this case the testis had returned to its normal size and consistency after

An Aid to Litholapaxy

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Removal of the crushed fragments of stone at the end of a litholapaxy is often performed by using a wide bore cannula, but there are many advantages in using a visualising instrument such as the resectoscope; not only is the sheath straight and of wide bore, but the bladder may be examined to ascertain the size and position of any retained fragments.

Removal of the few final fragments often presents difficulties and attempts to use a standard resectoscope loop to manipulate these fragments often leads to bent and broken loops and much frustration.

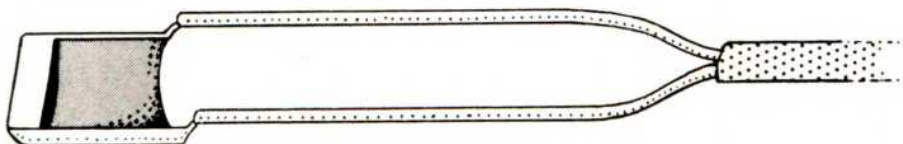


Fig. 1. Close-up of stone extractor.

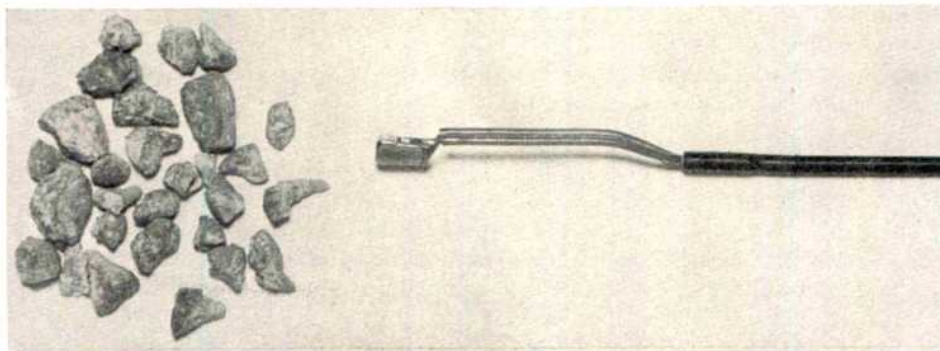


Fig. 2. Extractor with calculi removed from a typical case.

The modified loop illustrated (Fig. 1) was devised to aid manipulation of stone fragments, and is useful even when they are adherent to the bladder wall. Small fragments can be manipulated through the sheath; larger pieces may occasionally be impacted into the end of the resectoscope which is then removed together with the contained fragment. Illustrated (Fig. 2) is a collection of fragments removed from one patient and the instrument has been used on several other occasions with satisfactory results.

The modified loop or scoop is manufactured by the G. U. Manufacturing Company, 33 Devonshire Street, London WIN 2AJ, and my thanks are due to Mr Walter Wood of that company for help in development.

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Mechanical Assistance in Urological Surgery

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Mechanical assistance at operation frees the assistant's hands for skilled activity—and incidentally also eliminates the disadvantages of fatiguing the assistant by his having to retract for long periods.

An instrument (the "Mechanical Assistant") has been designed which provides retraction and other static functions at operation.

The Mechanical Assistant

The Mechanical Assistant (M.A.) (Fig. 1) has 3 components: 1. A conical stem post which is clamped to the side rail of the operating table.

2. A flexible arm consisting of a number of separate segments which are held together by means of a Bowden cable which passes through the centre of each in the manner of a string of beads; when the Bowden cable is slack the segments can be moved in relation to one another and the instrument is flail; when the cable is made taut by a "wind-in, wind-out" screw mechanism, the segments are forcibly drawn together, whereupon the instrument becomes rigid maintaining the shape it was placed in when flail.

3. A universal chuck in which retractors, endoscopic instruments and other accessories can be held in any position determined by the surgeon.

Method of Use

In use the conical stem post, not sterilised, is first secured on the operating table side rail at a site appropriate to the operation before the patient is prepared; when the patient is towelled up the drapes are so positioned that the stem post is left exposed; the surgeon then places the flexible arm, previously sterilised by autoclaving, over the stem post on to which it is guided by means of a centring screw.

Retractors or other instruments are inserted and held in the M.A. appropriate to the requirements of the operation. When a retractor is placed in the operating area and satisfactory exposure obtained, the M.A. is made rigid by tightening the Bowden cable; the retractor will now remain as positioned, effectively doing the work of an assistant until the requirements of the operator change as the operation proceeds; the retractor can then be repositioned in the operating field again by first slackening and then tightening the Bowden cable.

The M.A., by virtue of its universal chuck, is capable of holding endoscopic instruments and a complete range of retractors for all purposes. It requires no special servicing or mechanical aptitude to use.

There are available a number of accessories designed to be held in the universal chuck to assist the surgeon in such tasks as holding endoscopes, syringes, suckers, haemostats whilst ligaturing bleeding points and suturing during the performing of an anastomosis (see Table).

In the following circumstances the Mechanical Assistant is of great value in the performance of urological procedures by virtue of its universal chuck and other accessories.

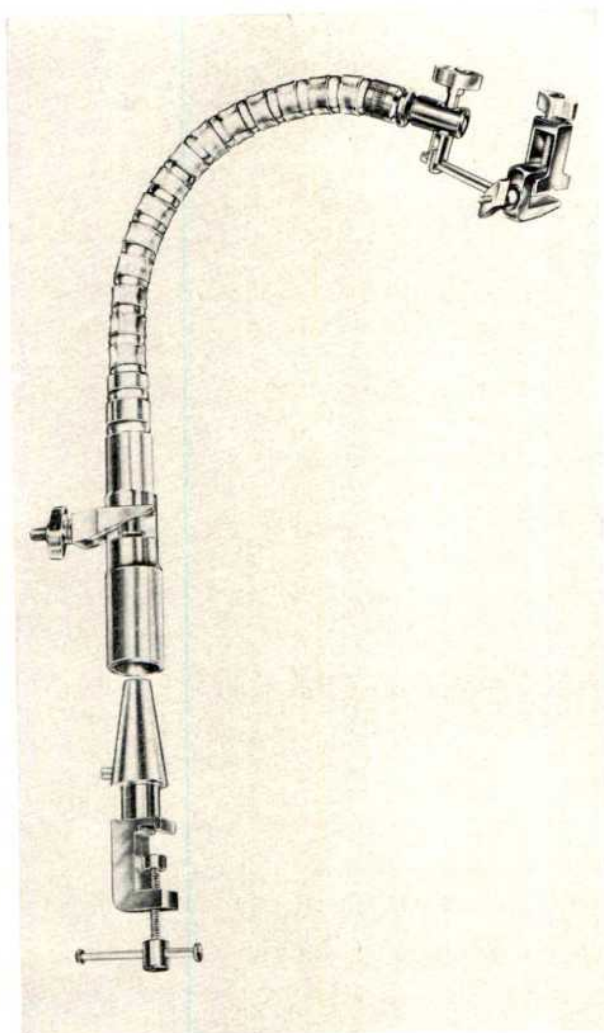


Fig. 1. The Mechanical Assistant.

Table

Available Accessories which extend the Applicability of the Mechanical Assistant

The Mechanical Assistant	Single hook	Instrument tray
Suture holder	Sucker arm	Amputation sling
Haemostat holder	Endoscope cradle	Kidney sling
Row of hooks	Syringe holder	

Retraction

Mechanisation of retraction (among other aspects of assisting) is a particularly desirable innovation in surgical technique.

The chuck of the Mechanical Assistant is described as universal in that it is capable of receiving and holding all the stock retractors of various designs without the need for special retractors for this purpose (Fig. 2).

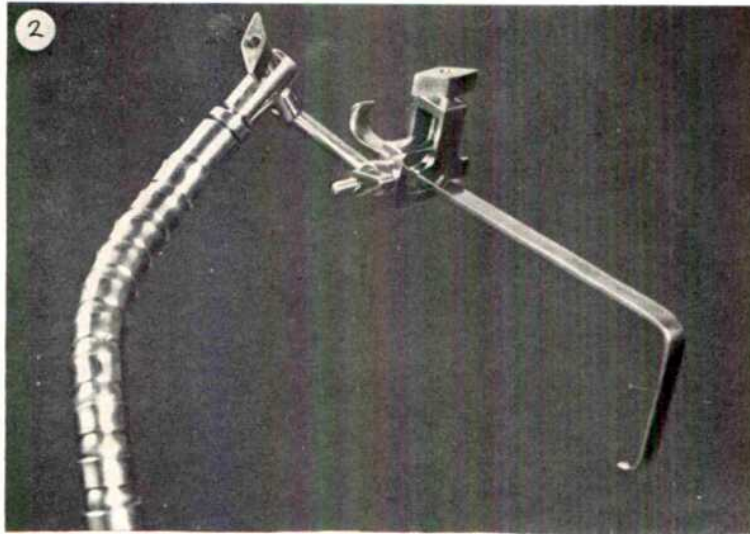


Fig. 2. The Mechanical Assistant through its universal chuck can hold a complete range of standard retractors.

Suction

Suction during prostatectomy can be surrendered with advantage to the M.A. leaving hands free to take a more active part in the procedure.

Endoscopic Sling

During lengthy endoscopic procedures—or when assistance is inadequate—it is a boon for the surgeon to be able to take his hands away from the endoscope from time to time in order to rest his arms or to enable him to serve himself from the instrument trolley.

The endoscope sling (Fig. 3) achieves this objective in that without clamping, and therefore without risk of damaging the instrument, the endoscope is supported in any position determined by the surgeon for as long as he requires.

The endoscope sling is also particularly useful when, during ureteric catheterisation for retrograde pyelography, the catheter can be passed only a short way up the ureter and it is necessary to take the X-rays with the cystoscope remaining *in situ*. The surgeon is thus enabled to keep his hands clear of the radiation field while the X-rays are being taken.

Kidney Sling

One method of supporting the kidney during operation is, of course, to pass linen tape around both poles and clip the ends in a haemostat which the assistant then holds. The kidney sling

(Fig. 4) accomplishes the same objective somewhat more conveniently. It consists of 2 metal ellipses, one swivelled inside the other at a joint eccentrically placed. A fine chain by which the sling is suspended is looped through the ellipses. To use, one of the ellipses of the sling is placed under

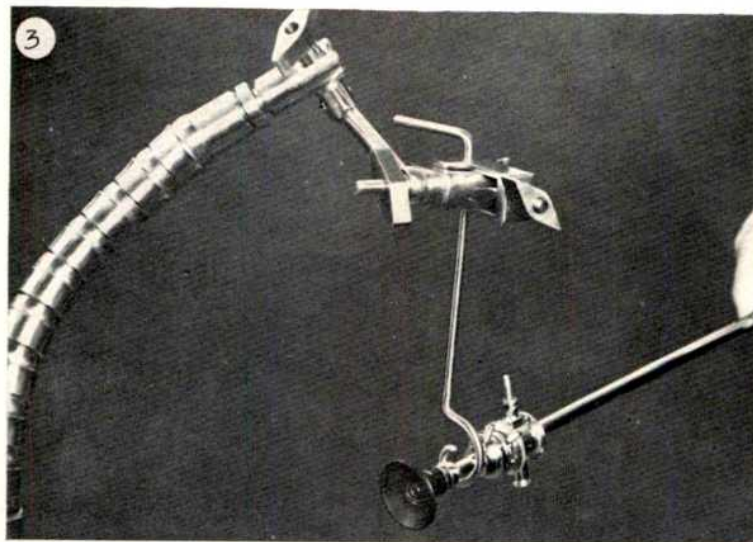


Fig. 3. The endoscope sling.

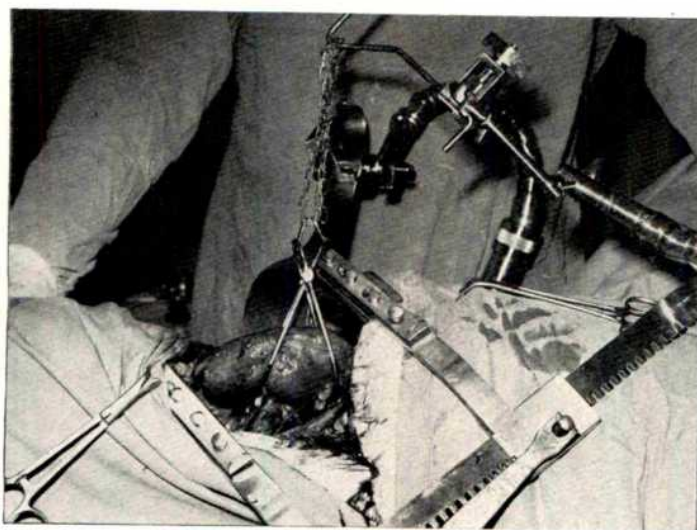


Fig. 4. The kidney sling in action during a partial nephrectomy.

each renal pole after the kidney has been mobilised. The suspensory chain is then slung from the chuck of the Mechanical Assistant which is then adjusted to support the kidney in the required position.

A subsidiary action of the suspensory chain is gently to approximate the ellipses thus preventing them from slipping out of position.

The X-ray film that is placed in the wound in juxtaposition to the kidney, for radiography during operation for renal calculi, can be held by the M.A. so that members of the operating team can avoid unnecessary exposure to radiation.

Summary

An apparatus (the "Mechanical Assistant") has been designed to increase the efficiency and to remove the tedium of surgical assisting. It also enables a surgeon to operate single-handed if circumstances make it necessary.

The apparatus facilitates protection of the surgical team during radiographic procedures.

This instrument has been developed with the generous co-operation of Mr R. Pickering of Polar Hydraulics Ltd., Tamworth and is available from Down Brothers, Mayer and Phelps Ltd., Church Path, Mitcham, Surrey.

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The Use of Pentazocine as a Strong Analgesic in Urological Practice

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The problems of pain relief concern every doctor involved in clinical practice but for patients in urological practice there are additional difficulties concerned with their age and cardiovascular state. Pentazocine (Fortral) is a potent analgesic which is being increasingly used in clinical practice as a substitute for the opiates. It produces good cardiovascular stability (Scott and Orr, 1969; Kay, Keaney and Taylor, 1970; Stephen, David and Scott, 1970; Scott and Adgey, 1971) and is free from the D.D.A. restrictions.

Pentazocine has been widely investigated in clinical practice (see review article Potter and Payne, 1970) and has also been investigated in urological practice (Anderson *et al.*, 1966; Wilkey, Barson and Rowe, 1967). The renal haemodynamics have been studied by Sigman and Elwood (1967).

As part of an overall assessment of the place of pentazocine in urological practice an analgesic comparison with pethidine was carried out involving patients suffering from renal colic and those who were in pain after urological surgery.

Material and Methods

A total of 77 patients were included in this double-blind between-patient comparison of pentazocine 40 mg and pethidine 100 mg. All the patients were suffering from renal colic or had recently undergone urological surgery. Pregnant patients, patients known to be taking monoamine oxidase inhibitors and those with a blood urea greater than 100 mg per 100 ml were excluded from the study.

On admission to the trial a brief patient history was recorded and the degree of pain assessed by the observer on a 4-point scale, nil (0), mild (1), moderate (2), or severe (3). The patient was then given an intramuscular injection of pentazocine or pethidine according to the pre-determined random code: further assessments of the pain intensity were made at hourly intervals for the next 4 hours. At these times the patients themselves were asked to assess the severity of the pain as "less than", "the same as" or "worse than" that before the injection. Patients who were asleep at the time of the assessment were not given a pain score by the observer. Side-effects which were spontaneously reported by the patients were noted, but no leading questions concerning side-effects were put by the observer.

Results

Tables I, II and III show the age, weight and cause of the pain in all the patients in the 2 drug groups. Although there was a higher proportion of males in the pethidine group than in the pentazocine group this difference was not significant at the 5 per cent level and in all other respects the 2 drug groups were similar. One male patient in the pentazocine group received a bronchodilator drug during the period of the study.

Table IV shows the observers' assessment of the pain intensity before injection of the trial drug.

Table I
Age Distribution

Drug	Sex	Age (years)						Total
		29	30—	40—	50—	60—	n.s.	
Pentazocine	M	1	4	4	9	4	—	22
	F	—	6	3	4	—	—	13
Pethidine	M	3	4	7	8	6	2	30
	F	1	3	2	3	3	—	12
Total		5	17	16	24	13	2	77

n.s. = Not stated.

Table II
Distribution of Weight and Sex

Drug	Sex	Weight (stones)						Total
		9	9—	10—	11—	12—	13—	
Pentazocine	M	2	3	5	7	3	2	22
	F	3	3	4	1	2	—	13
Pethidine	M	3	10	4	8	3	1	30
	F	2	6	2	1	—	1	12
Total		10	22	15	17	8	4	77

n.s. = Not stated.

Table III
Cause of Pain

Drug	Sex	Diagnosis				Total
		A	B	C	D	
Pentazocine	M	7	3	5	7	22
	F	6*	5	1	1	13
Pethidine	M	9	5	8	8	30
	F	4	5	2	1	12
Total		26	18	16	17	77

* = One patient had a right pyelolithotomy with a partial nephrectomy.

A = Upper urinary tract surgery.

B = Nephrectomy.

C = Lower urinary tract operations (bladder repair, prostatectomy, orchidectomy, laparotomy).

D = Pain due to "renal" (ureteric) colic.

Table IV
Observer's Assessment of Pain Intensity Before Injection

Drug	Pain Intensity				Total
	Slight	Moderate	Severe	Not Stated	
Pentazocine	1	20	14	—	35
Pethidine	—	22	19	1	42
Total	1	42	33	1	77

Table V
Mean Pain Reduction Score (Observer's Assessments)

Drug	Mean Pain Reduction Score at Time:			
	1 hr.	2 hr.	3 hr.	4 hr.
Pentazocine	1.4 (n = 24)	1.4 (n = 22)	1.2 (n = 22)	1.3 (n = 21)
Pethidine	1.6 (n = 27)	1.7 (n = 28)	1.7 (n = 30)	1.5 (n = 32)

Table VI
Patient's Assessment of Change in Pain Intensity

Drug	Patient's Assessment of Pain at:																			
	1 hr.					2 hr.					3 hr.					4 hr.				
	-1	0	A	n.s.		-1	0	+1	A	n.s.	-1	0	+1	A	n.s.	-1	0	+1	A	n.s.
Pentazocine	15	4	15	1	12	5	1	12	5	16	4	1	12	2	10	5	2	15	3	
Pethidine	22	2	15	3	19	4	—	16	3	24	3	—	10	5	23	4	1	5	9	
Total	37	6	30	4	31	9	1	28	8	40	7	1	22	7	33	9	3	20	12	

Key: -1 = Less pain than before injection.
 0 = No change.
 A = Asleep.
 n.s. = Not stated.

At each assessment after injection of the analgesic drug a pain reduction score was calculated for each patient by subtracting the score for pain intensity (0, 1, 2 or 3) from the initial pain intensity. If the pain intensity was greater after the injection than before, the pain reduction was scored zero, indicating no reduction. Table V shows the mean pain reduction scores in each drug group at each assessment period together with the number of patients on whom the assessment

could be made. At each assessment the mean reduction score was slightly greater for pethidine than pentazocine but this difference was not significant at the 5 per cent level.

Table VI shows the patient's own assessment of the difference in pain intensity after injection compared with the initial severity and again there is no statistically significant difference between the 2 drug groups in the first 3 hours. At the fourth assessment, however, more patients in the pethidine group had less pain after the injection than in the pentazocine group, and this difference is significant ($P < 0.005$).

Side-effects

Three patients in the pentazocine group complained of nausea compared with 5 patients in the pethidine group who complained of nausea, in some instances associated with dizziness. No other side-effects were reported.

Discussion

The basis of most therapeutic régimes for pain relief has been opium or its refined derivatives (Archer and Harris, 1965; Ayd, 1967; Potter and Payne, 1970). Despite the obvious advantage of such compounds, they all have a problem with respect to drug addiction. Pentazocine is a drug which has not been reported as yet to have strong addictive liabilities despite its widespread use since its introduction in the mid-sixties (Archer *et al.*, 1964; Bellville, 1964; Cass, Frederik and Teodoro, 1964; Keats and Telford, 1964; Bellville and Green, 1965; Ende, 1965; Beaver *et al.*, 1966; Eddy, 1966; Hinshaw *et al.*, 1966). The equivalent analgesic potency of the drug is: Pentazocine 30 mg to Morphine 10 mg to Pethidine 75-100 mg.

The drug has been used as an intramuscular injection in a wide variety of clinical conditions, *e.g.* in postoperative pain, in general surgery (Gordon and Moran, 1965; Sadove and Balgot, 1965; Conaghan *et al.*, 1966; Erb, 1966; Finestone and Katz, 1966; McSwan *et al.*, 1966; Scott, Abernethy and Livingston, 1966), in gynaecological surgery (Coddens, 1966), in obstetrics (Filler and Filler, 1966; Duncan, Ginsberg and Morris, 1969), in proctology (Marks, 1967), in oto-rhino-laryngology (Mounier-Kuhn, 1969). There are a few publications which relate to the use of the drug specifically in urological practice (Anderson *et al.*, 1966; Wilkey, Barson and Rowe, 1967; Takeuchi, 1969) where the patient's age related to respiratory and renal function has special significance with respect to the use of strong analgesics.

This trial confirmed the findings of our earlier study (Scott, Abernethy and Livingston, 1966) involving patients in pain after general surgery and in which we compared 20 mg pentazocine with 50 mg pethidine: the same ratio was used in the present study and the results showed that pentazocine was as effective as pethidine, but with a slightly shorter duration of action. This is in accord with the findings of Guldman and Sestoft (1969) who showed 40 mg pentazocine to be slightly more effective than 100 mg pethidine and those of Kay, Keaney and Taylor (1970) who found the duration of action of pentazocine to be slightly shorter than that of the opiates.

At each of the assessments approximately a third of the patients in both groups were asleep and so the intensity of their pain could not be assessed. Although sleep does not necessarily indicate that the patient is free of pain it might be assumed that whereas pain had previously kept the patient awake, the onset of analgesia had dulled the pain sufficiently to allow the patient to go to sleep. This point may well be important in the interpretation of the sedative effects of analgesics. Norris and Telfer (1968) found that the sedative effects of 20 mg pentazocine were almost the same as those of 10 mg morphine and O'Connell *et al.* (1968) found pentazocine to produce less sedation than pethidine. In a more recent comparison of pentazocine and pethidine, Tammisto and Takki (1971) also found significantly greater sedation in the pethidine-treated group so our results are difficult to explain. The finding that more patients in the pentazocine group were asleep at the 3- and 4-hour assessments may in fact be a result of better pain relief in this group.

The patients may thus have been able to obtain natural sleep rather than have this as a true drug effect.

Conclusion

This study has confirmed the effectiveness of pentazocine as an analgesic for the relief of pain from renal colic and in urological surgery. The good cardiovascular stability reported by other workers would seem to be a particular advantage in urological practice where many of the patients are elderly, hypertensive and prone to suffer from myocardial ischaemia or infarction. The widespread use of the drug in treating renal colic may reveal any tendencies which the drug might have to produce addiction; experience with previous analgesics in this field, especially pethidine, should be remembered. Further work with respect to the effects of pentazocine on blood pressure and respiratory rates is being undertaken in this department.

Summary

In a double-blind between-patient study the analgesic efficacy of pentazocine and pethidine was compared in urological practice. There were no statistically significant differences between the 2 drug groups although the duration of action of pentazocine seemed to be slightly shorter than that of pethidine. Side-effects were infrequent with either drug and it was concluded that pentazocine is a suitable alternative to pethidine in urological practice.

We are grateful to Mr T. Muir, lately of Winthrop Laboratories, for his help and assistance in this work.

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Short Case Reports

Reno-Broncho-Pyelo-Cutaneous Fistula

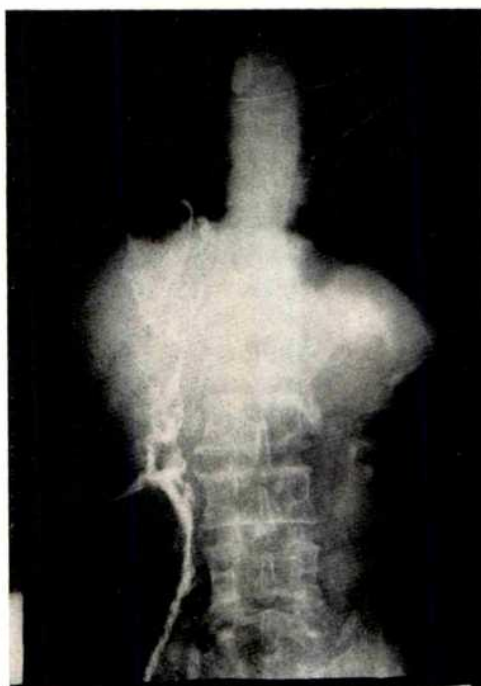
A. A. ALVI, T. C. GOEL and P. C. DUBEY

K. G. Medical College, Lucknow University, India

The patient was a man aged 60 years. A year previously an abscess in the right loin had been drained. A sinus with an intermittent purulent discharge persisted. Nine months later he developed a cough with purulent sputum.

Investigations. There was pyuria, culture giving a growth of *E. coli*. I.V.P.—a right staghorn renal calculus with no sign of function on this side. *Sinogram* (Fig.)—a track led from the skin into the renal pelvis with free flow down the ureter and through the upper pole of the kidney and the diaphragm into a cavity communicating with the lower bronchial tree. Injection of methylene blue into the skin sinus rapidly appeared in the sputum and in the urine.

Operation. Exploration through the bed of the 11th rib showed the cavity to contain about 250 ml of necrotic material. The cavity was evacuated, the kidney removed and the diaphragm closed. Recovery was almost complete within 15 days, and 3 months after operation X-ray of the chest showed obliteration of the cavity in the lung.



Sinogram showing communication, above with right lung, and below with patent ureter.

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Cystitis Emphysematosa

AL. ANNAMALAI, S. SHREEKUMAR and T. V. ULAGANATHAN

General Hospital, Madras

In a 38-year-old diabetic woman with *E. coli* urinary infection radiographs showed bilateral renal calculi and a thin ring of gas outlining the bladder wall (Fig. 1). Cystoscopy revealed small vesicles in the mucosa. In another diabetic (aged 40, male) X-ray showed a gas "bead-necklace" in the bladder wall (Fig. 2). This film incidentally shows segmented calcified vasa deferentia, typically seen in severe diabetes.

Cystitis emphysematosa is a rare, benign, reversible inflammation of the bladder with gas-filled cysts in the wall. It occurs mostly in diabetics. There is no specific symptomatology except that due to co-existing nephrolithiasis, glomerulonephritis, cystitis or haematuria. Bladder wall gas has been seen in virulent infections and may be due to enzymes acting upon tissue glucose. Management is directed towards the primary condition. Cystitis emphysematosa in itself does not affect the prognosis.

Reference

BAILEY, H. (1961). Cystitis emphysematosa. *American Journal of Roentgenology*, 86, 850-862.



Fig. 1. Radiograph showing thin translucent ring of gas outlining the bladder.

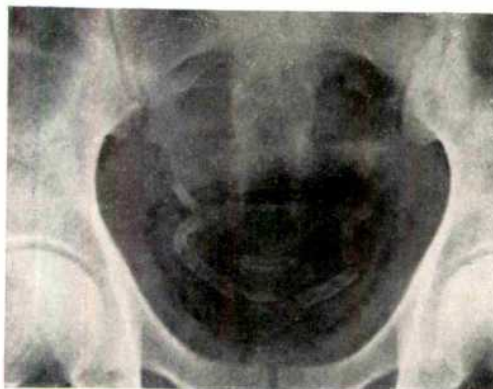


Fig. 2. Radiograph showing gas bead-necklace outlining the bladder. Also segmented calcified vasa deferentia.

Book Reviews

Common Problems in Office Practice: Current Methods of Diagnosis and Management. By ROBERT B. TAYLOR. Pp. 377. New York: Harper & Row, 1972. \$9.95.

The avowed intention of this book is to arm the young family physician for his work in the community at large, using only the simple diagnostic aids that he may manage himself. It eschews the irrelevant exotica of the traditional undergraduate textbooks.

Only 17 pages are occupied by the section on urological disorders, with the addition of 2 not particularly well chosen pages of references for the intended readership. Enuresis, haematuria, infection and calculus are reasonably well presented on a simple practical level, but the management of prostatic disorders is more contentious. In particular many would take exception to the advice that indwelling catheters should be irrigated daily with saline.

Perhaps the greatest fault of this section of the book is its omissions. Subjects such as circumcision in infancy, epididymo-orchitis and torsion of the testis are not uncommonly of concern to the general practitioner. The other 95 per cent of everyday practice is dealt with in a similar fashion, and most of us, whatever our particular niche, can learn something useful from its pages.

J. C.

The Principles of Transurethral Resection and Haemostasis. By J. P. MITCHELL. Pp. XII + 262 with 124 illustrations. Bristol: John Wright & Sons Ltd. 1972. £6.00.

Transurethral resection of the prostate is steadily becoming a more popular operation with urologists in England. In this book there is a comprehensive description of the indications, contra-indications and complications of transurethral resection. Additional chapters describe the relevant anatomy, the instruments used and the basis of surgical diathermy. The author's technique for transurethral resection of the prostate is fully described and emphasis is placed on meticulous haemostasis. Mr Mitchell also describes the role of transurethral resection in dealing with bladder neck obstruction in the male, female and child, bladder tumours and the neurogenic bladder.

This book is essential reading for all trainees in urology and of value to all those who should use a resectoscope.

J. P. P.

Renal Transplantation Theory and Practice. By JEAN HAMBURGER, M.D., JEAN DORMONT, M.D., and JEAN-FRANCOIS BACH. Pp. 326 with illustrations. London: Churchill. 1972. £7.00.

As its title suggests this excellent book covers fully the theoretical and practical aspects of renal transplantation and presents the view of the group working at the Hospital Necker in Paris.

There is extensive discussion of the experimental background and theoretical basis of transplantation biology, immunology and immunosuppression. However, practical aspects such as the choice of donor and recipient, kidney preservation and the pre- and post-operative management of the recipient are also covered. There are some areas where the views expressed are not universally accepted *e.g.* the role of steroids in immunosuppression and azathioprine toxicity in renal failure. Following the main body of the book there are appendices dealing with detailed methods of tests such as determination of HL-A antigen and mixed lymphocyte cultures.

The English translation is good and the book as a whole is an excellent insight into the philosophy of renal transplantation, which will be read with pleasure by all involved in renal transplantation and many outside the field.

D. R.

The Porphyrrias. By J. LYNDAL YORK, Ph.D. Pp. 126. Springfield, Ill.: Charles C Thomas, 1972. £4.83.

The porphyrias are a highly specialised subject, and at first glance would seem to have little interest for the specialist in nephro-urology. However, the presenting features of the acute porphyrias, most commonly acute intermittent porphyria, may bring the patient either to the urologist or the nephrologist. The severe abdominal pains may simulate renal colic or the homeostatic disturbances associated with the mental confusion and a raised blood urea may lead to the vague diagnosis of "uraemia".

This monograph presents a simple review of the development in the understanding of the porphyrias and is fully referenced. The metabolic abnormalities which may occur are discussed in considerable detail.

The emphasis of the book is mainly biochemical. To discuss the various types of porphyrias that occur the 1963 International Classification is used, with the main separation into the hepatic porphyrias and the erythropoietic porphyrias. The importance of drug induced acute attacks is stressed and one is reminded of the interesting feature that the porphyrias do not become overt until after puberty. This suggests that the sex hormones have an important part to play in accelerating the metabolic abnormality; again this is seen in women with the relationship of acute attacks of porphyrias during menstruation.

Curiously there is very little information to be gained from the book on how to diagnose an acute attack of porphyria from relatively simple tests. That an acute attack can occur without any discolouration of freshly passed urine is certainly not obvious from reading the text. There is a good factual assessment of the various forms of treatment. For the nephrologist the inappropriate secretion of anti-diuretic hormone with the associated hyponatraemia, and possibly hypomagnesaemia, in acute attacks often associated with a raised blood urea, is of considerable interest. This is particularly so where there is striking evidence for the beneficial therapeutic effect of large doses of carbohydrate administration. It has been suggested that 300 g of fructose or glucose in a 10 per cent solution should be given in 24 hours. Obviously, in the presence of water intoxication due to inappropriate A.D.H. secretion such a therapy could well be harmful, particularly as it has been claimed that the hyponatraemia is largely responsible for some of the central nervous system manifestations. As is usually the case the appropriate A.D.H. secretion results not only in a retention of water but also a relative sodium loss in the urine. The lowered plasma zinc concentration which has been described is thought to be due to urinary zinc loss; it has been suggested that the low plasma zinc may inhibit the action of lactic dehydrogenase resulting in the finding of the raised lactic acid in the plasma.

This is a valuable review monograph for anybody interested in metabolic diseases. It would be greatly improved by a discussion of the practical steps in diagnosis for the practising clinician.

A. M. J.

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Short case reports

Brief reports (preferably with 1 and not more than 2 illustrations) of unusual cases not published elsewhere may be submitted as summaries of not more than 200 words for consideration for publication as Short Case Reports. They should comprise (1) a Title, (2) Case description and (3) a brief Comment. The authors and references are each limited to 3. The titles of these reports will usually be recorded in *Index Medicus* and by MEDLARS.

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Clinicians who have ideas for research projects, but have no opportunity for carrying them out, may submit them for publication in the above section. The communication should not be longer than 500 words. References will be limited to 6.

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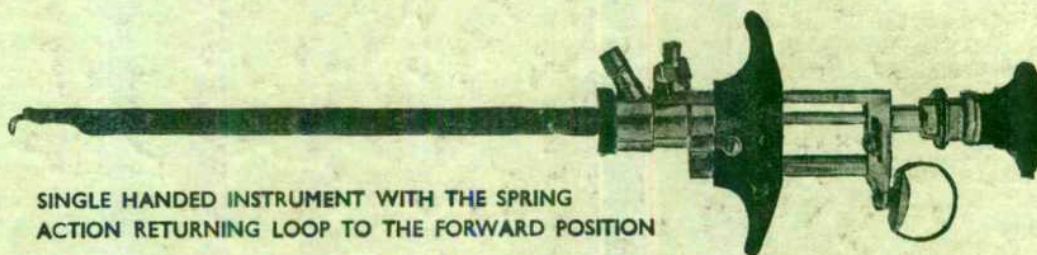
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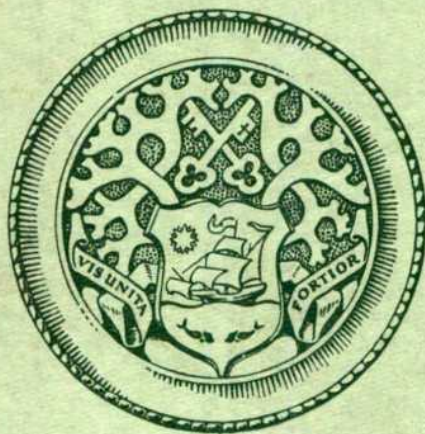
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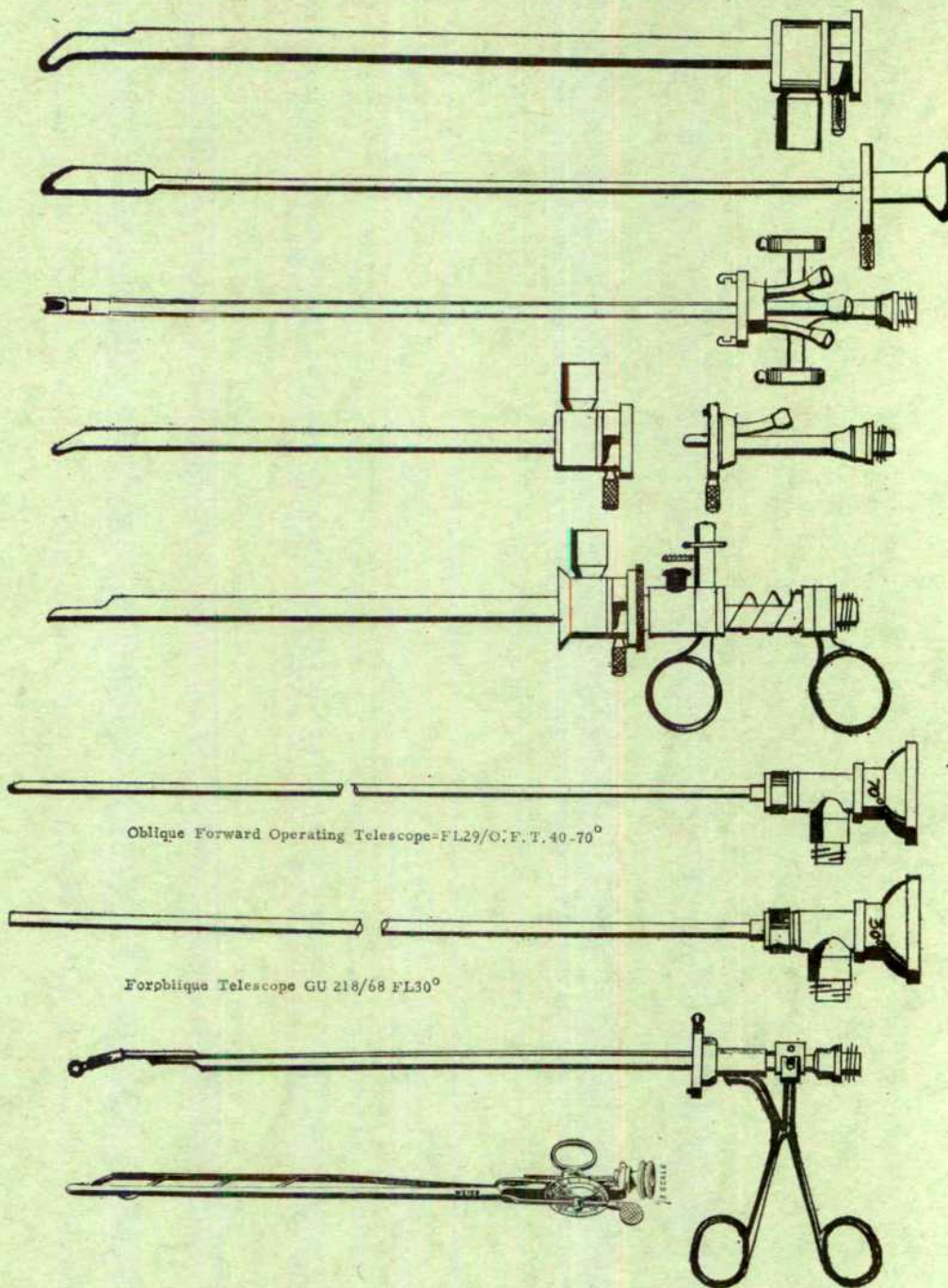


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TERENCE J. MILLIN, 1951
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LESLIE N. PYRAH, 1959
CUTHBERT E. DUKES, 1960
DAVID BAND, 1962



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(1) *Postgrad med J.* (1971), (September Supplement), 47, 7.

(2) *Brit med J.* (1969) *i*, 541.

(3) Leading Article, *Brit med J.* (1969), *i*, 525.

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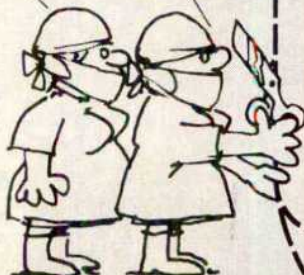
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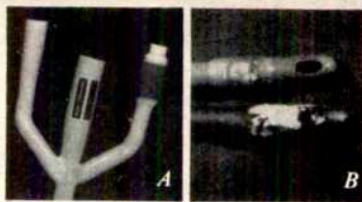
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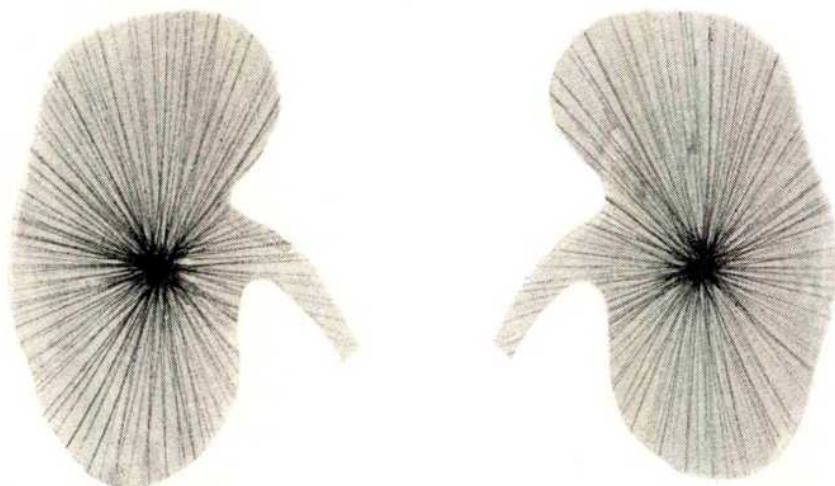
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1. Brit J Urol, (1973), **45**, 136.
2. J Clin Endocrin Metab, (1968), **28**, 1829.
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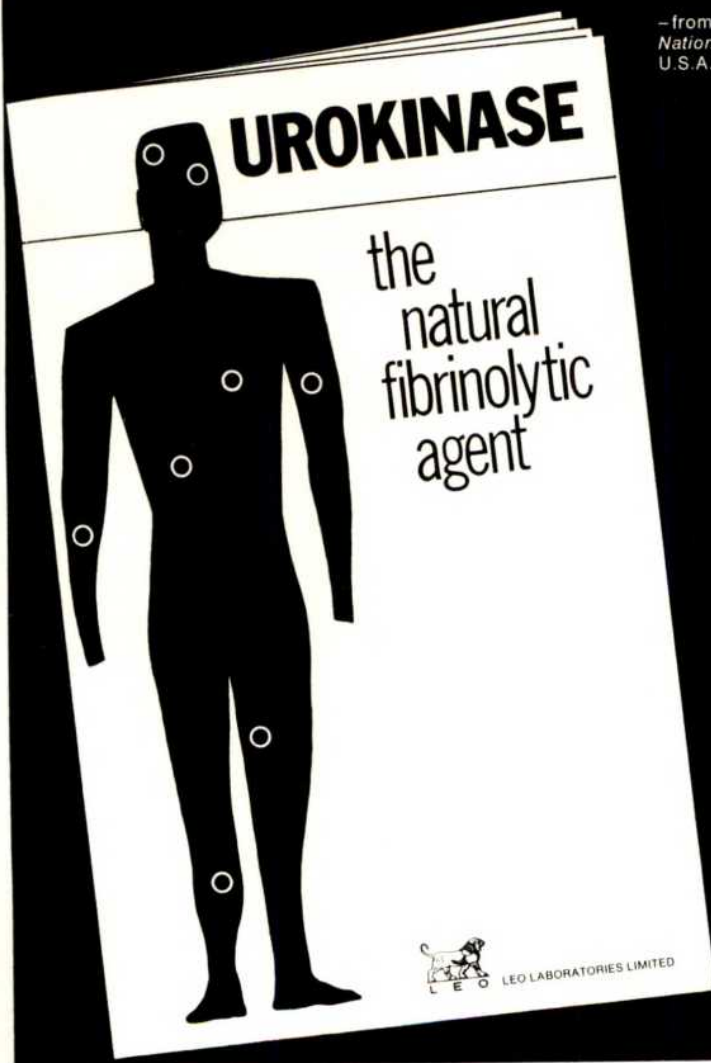
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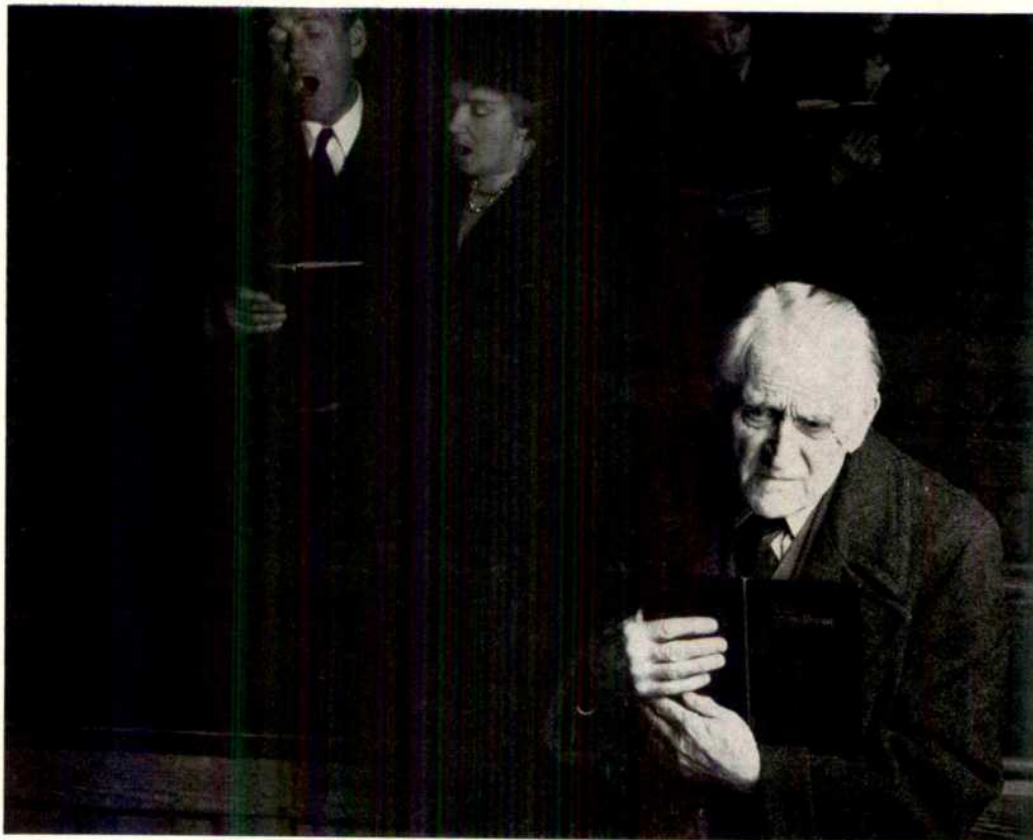
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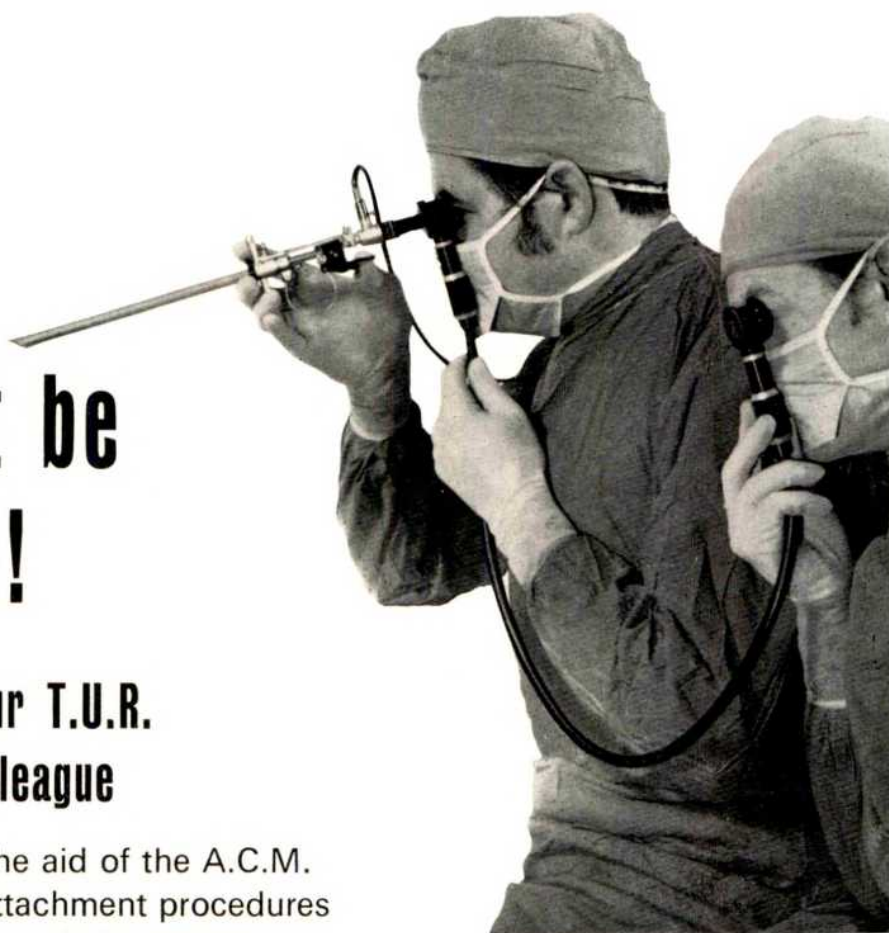
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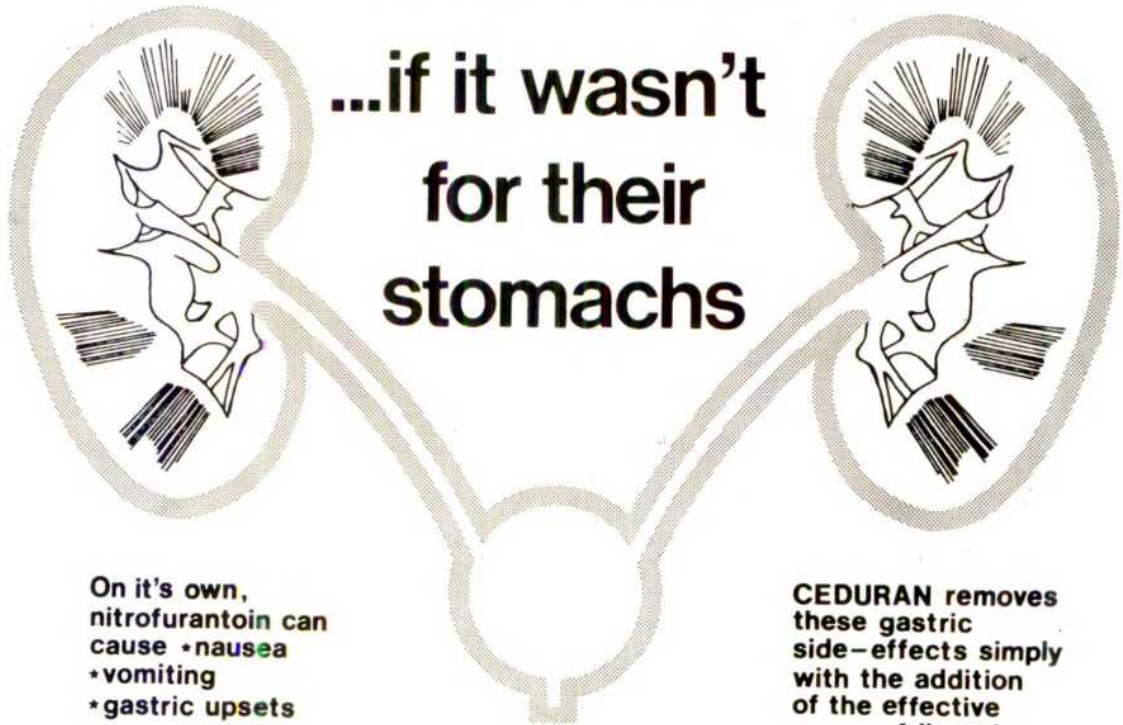
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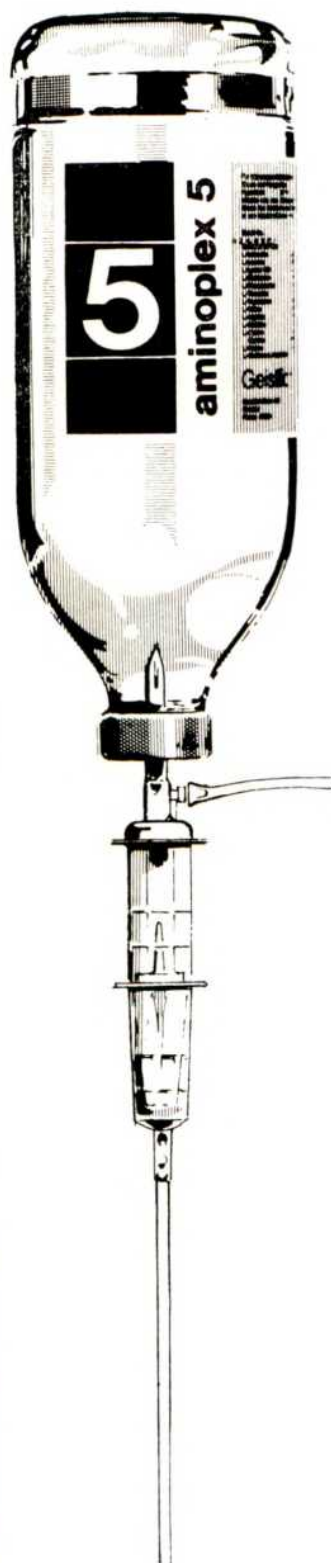
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Adjuvant Therapy for Adenocarcinoma of the Kidney: Present Position and Prospects¹

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Although the only hope of cure for patients with adenocarcinoma of the kidney rests with nephrectomy, this operation fails to prevent death from this disease within 5 years in at least 50% of surgical cases. Attention is now being directed to ancillary methods of treatment which may augment or assist the main surgical attack on the primary tumour, and thereby prevent or delay the development of local recurrence and distant metastases. The present communication is concerned with these methods which may be considered under 4 principal headings (Table I).

Table I

Adjuvant Therapy for Renal Carcinoma

1. Radiotherapy	3. Hormones
(a) Pre-operative	(a) Progestins
(b) Postoperative	(b) Testosterone
2. Cytotoxic drugs	4. Immunotherapy

Radiotherapy has long been used in conjunction with surgery for renal cancer, but in recent years its value and precise timing in the treatment of this tumour has become a subject of wide controversy. There has been mounting interest in the role of prophylactic chemotherapy for renal tumours aimed chiefly against occult metastases: the possible value of cytotoxic and hormonal agents for this purpose is now being assessed from their effect in advanced cases. Attempts to control cancer by immunological methods are being explored by many investigators throughout the world. Cases of renal tumour have attracted special attention because certain aspects of their natural history suggest the existence of host defence mechanisms for which supportive laboratory and clinical evidence is now emerging.

Radiotherapy

Carcinoma of the kidney is generally regarded as being a highly radio-resistant tumour. This view is undoubtedly correct in that the majority of such tumours do not show a good response to irradiation, as judged by a substantial reduction in size. However, this is not to deny that tumour cell viability may be significantly altered by irradiation and that some benefit can be derived from such treatment. Even a limited response may increase tumour mobility prior to nephrectomy, and perhaps reduce the risk of local recurrence and distant metastases resulting from spill of malignant cells at operation. The greater or lesser response to irradiation observed in some primary renal tumours or their metastases support this view.

¹ Based on a guest lecture to the New England Section, American Urological Association, Estoril, 11th October 1971.

Nearly 40 years have elapsed since Waters (1935) described cases of renal cell cancer in which, following irradiation, large tumours became smaller, less vascular and more mobile. It was not until 1951, however, when Riches and his colleagues in England reported higher survival rates in patients receiving postoperative irradiation, that greater interest was shown in radiotherapy for this disease. Since that time sporadic reports have appeared describing favourable responses

Table II

Five-year survival rates for patients with renal cell carcinoma treated by nephrectomy alone (S), or by nephrectomy and post-operative radiotherapy (S + R). Various authors (1951–1971).

Author	Treatment	Cases	5-year survival (%)	
Riches <i>et al.</i> (1951)	S	345	30	
	S+R	53	49	
Charteris (1951)	S	29	28	
	S+R	14	36	
Flocks and Kadesky (1958)	S	56	48	
	S+R	40	52	
Ringleb and Rommel (1963)	Total	S	44	29
		S+R	45	55
	By dose	< 3000R	21	48
		> 3000R	24	62
Bratherton (1964)	S	35	29	
	S+R	21	43	
Arner <i>et al.</i> (1966)	Total	S	127	61*
		S+R	20	53*
	Grade II†	S	108	60*
		S+R	14	69*
Flocks (1968)	S	287	39	
	S+R		44	
Peeling <i>et al.</i> (1969)	S	96	52	
	S+R	68	25	
Cox <i>et al.</i> (1970)	S	58	45	
	S+R	28	32	
Rafla (1970)	S	94	37	
	S+R	81	56	
Skinner <i>et al.</i> (1971)	S	190	57	
	S+R	18	50	

* Corrected results.

† Medium and high malignancy.

of the primary tumour to irradiation, or improved survival rates following postoperative treatment compared with nephrectomy alone (Delorme and Ballanger, 1960; Reboul *et al.*, 1962; Ringleb and Rommel, 1963; Windeyer and Riches, 1964; Bratherton, 1964; Păces, Placherova and Capek, 1964; Riches, 1970; Rafila, 1970) (Table II).

Enthusiasm for radiotherapy in cases of renal cell cancer has been greater in Europe than in

America. The reputation of radio-resistance and the frequency of tumour deaths from distant metastases are undoubtedly responsible for the reluctance of many American urologists to consider irradiation as an adjuvant to nephrectomy. For example, in the recent report by Skinner *et al.* (1971) postoperative irradiation was used in only 18 of 208 cases, whereas it seems to have been employed routinely in 75% of a sample of English centres surveyed by Bratherton (1964).

Planned irradiation with surgery may be given pre- or post-operatively.

Postoperative Irradiation

The value of routine postoperative irradiation for renal carcinoma, widely used for many years in some centres, is now being questioned. Most published series suggest that this treatment improves the prognosis compared with nephrectomy alone (Table II). The gain, however, is usually small and without statistical significance. Furthermore, the comparison of case-groups has generally not been on the basis of similar lesions.

It is not of course possible to make a proper comparison between 2 methods of treatment when results are assessed, not only by retrospective analysis but often without due regard to such important prognostic variables as the extent of the tumour and its histological grade

Table III

Incidence of histological tumour grades in three reported series of patients with renal carcinoma. Note the high proportion of low-grade tumours in Robson's cases. Treatment results cannot be compared without reference to grade and stage.

Grade	Robson <i>et al.</i> (1969) 79	Riches (1964) 110	Myers <i>et al.</i> (1970) 508
	%	%	%
I	62	46	21
II	19	36	50
III	19	18	29*

* III+IV.

(Bloom, 1965). For example, in 3 recent reports concerning cases of renal cancer there was a considerable difference in the distribution of tumour grades (Table III), and this must undoubtedly influence the over-all survival rates presented by each author. Thus, the superior results claimed for radical nephrectomy by Robson, Churchill and Anderson (1969) might be explained by the unusually high incidence of low-grade tumours in their series. Even when cancer cases are classified carefully by a system of staging, the resulting groups may not be sufficiently uniform to compare the merits of different treatments without reference to intrinsic tumour malignancy, particularly when dealing with cancers possessing a wide spectrum of biological behaviour (Bloom, 1965; Myers, Fehrenbaker and Kelalis, 1968; Bloom and Field, 1971).

It is important to stress that the absence of a generally accepted method of staging of renal carcinoma, and the frequent failure by authors to present results according to surgical and pathological findings, make comparison of treatment results within the same centre, let alone between different hospitals, completely futile.

Peeling, Mantell and Shephard (1969) from the London Hospital made efforts to compare treatment results in comparable groups of cases and found that postoperative irradiation did not increase survival. The adjuvant treatment, in fact, appeared to worsen prognosis (Table IV). It is difficult to explain this finding, which is at variance with the experience of most other

authors. No details of case-selection or of radiotherapy are presented for the London Hospital series which spans a quarter of a century (1940-1965) and also includes the administrative problems associated with hospital treatment during the war years. The underlying factors responsible for the exclusion of no less than 108 of 348 cases on the grounds of inadequate data needs examination. Were many of the rejected cases treated surgically at other hospitals, and only referred

Table IV

Renal Carcinoma: 5-Year Results
(London Hospital)

Group	S		S+R	
	Cases	Alive	Cases	Alive
		%		%
Local tumour spread (renal vein and/or extra-renal tissue)	37	38	40	13
Extra-renal spread only	15	52	18	0
Renal vein only involved	14	42	7	34
Low tumour grade	35	61	27	28
High tumour grade	24	54	23	9
All cases	96	52	68	25

Peeling *et al.* (1969).

Table V

Renal Carcinoma: 5-Year Results
(Manitoba Cancer Foundation)

Group	S		S+R	
	Cases	Alive	Cases	Alive
		%		%
Capsule involved	52	28	59	57
Renal vein involved	36	30	35	40
Renal pelvis involved	49	32	50	60
Renal pelvis and capsular tissue involved	21	33	25	85
All cases	94	37	81	56

Rafla (1970).

to the "London" for radiotherapy? If so, what was the policy of the outside referring surgeons, and that of the surgeons at the London Hospital itself with regard to selection of cases for post-operative irradiation?

The results reported by Peeling and colleagues (1969) are contrary to the general trend, and find no support in the recent detailed analysis carried out by Rafla (1970) in a series of comparable

size treated at the Manitoba Cancer Foundation (Table V). Rafla (1970) excluded only 1 patient from among 244 cases, and correlated prognosis with various pathological features. In patients with involvement of the renal pelvis or renal capsule, or of both these structures, there was a substantial and significant increase of survival following postoperative irradiation compared with nephrectomy alone (Table VI). Furthermore, the local recurrence rate after the combined treatment in 94 cases was only 7%, compared with 25% in 96 cases treated by surgery alone.

4 of the 11 different reports referred to in Table II show lower survival rates for cases receiving postoperative irradiation compared with nephrectomy alone (Arner *et al.*, 1966; Peeling *et al.*, 1969; Cox *et al.*, 1970; Skinner *et al.*, 1971). In 3 of these 4 studies the difference in survival or the number of cases receiving the combined treatment was small. This also applied to some of the reports showing an improved survival following the combined treatment.

Whilst it is clearly recognised that the case for adjuvant radiotherapy for renal cancer remains to be proven, the overall trend at the present time seems to favour postoperative irradiation (Table II). The results obtained in a substantial number of cases by Riches, Griffiths and Thackray (1951), Ringleb and Rommel (1963) and especially Rafla (1970), are particularly encouraging. The difference in favour of the combined treatment becomes more significant when it is

Table VI

Renal Carcinoma—Local Recurrence by Treatment

Treatment	Cases	With Local Recurrence
		%
Nephrectomy	96	25
Nephrectomy and radiation	94	7
Total	190	16

Rafla (1970).

appreciated that in such retrospective studies the more advanced cases have usually been referred for the adjuvant treatment. For example at the Royal Marsden Hospital, although the 3-year survival rates for nephrectomy alone and for nephrectomy and postoperative radiotherapy were practically identical, the incidence of unfavourable tumour features (renal vein or capsule involvement) was substantially greater in the group referred for the combined treatment (Table VII). In the series reported by Arner *et al.* (1966), 4 of 20 cases (20%) receiving postoperative irradiation had tumours of the highest grade of malignancy, compared with only 7 of 127 (5%) treated by nephrectomy alone. When cases of a more uniform grade in this latter series are grouped together, the results of the combined treatment appear more favourable (Table II).

It would be difficult to justify a randomised trial from which to assess the value of postoperative irradiation if such a study were to include cases with known gross residual disease. The question which remains to be answered, and one for which a clinical trial would be acceptable, concerns the value of routine prophylactic postoperative radiotherapy for cases in which total removal of the tumour appears to have been accomplished. If such a study were to be undertaken it would be necessary to consider what might be achieved by surgery alone in the most favourable cases of this group, and the possible risks incurred by adjuvant irradiation itself which, after all, may be unnecessary. Complications following postoperative radical irradiation are rare if doses are limited to 5,000 rads and are fractionated over not less than 6 weeks. On the other hand, it seems

that postoperative treatment can add little to the expectation of life in those patients with tumours of low-grade malignancy without evidence of local or regional spread, since Riches (1964) found that nearly 90% of such cases in his series were alive at 5 years.

Until the role of postoperative irradiation for renal carcinoma is established, what recommendations can be made regarding the management of patients not committed to clinical trials? From the available evidence there can be no objection, and indeed every reason, to recommend post-operative radiotherapy in the presence of gross residual disease. Such treatment also appears to be indicated when certain unfavourable pathological features are present in the surgical specimen, such as renal capsule invasion and perhaps high-grade malignancy *per se*. The regional lymph nodes are involved in about 25% of operable cases: in patients with tumours exceeding 6.5 cm the incidence reaches 50% (Hulten *et al.*, 1969). Whether a radical node dissection is carried out or not as part of the nephrectomy procedure (Robson *et al.*, 1969), postoperative irradiation would seem advisable in node-positive cases.

Table VII

**Renal Carcinoma—Survival by Treatment
(Royal Marsden Hospital)**

In this retrospective study of new cases without obvious distant metastases, the 3-year survival rates for nephrectomy alone and for nephrectomy and postoperative irradiation are comparable, but note the considerably greater incidence of unfavourable cases referred for irradiation. (Information regarding the state of the renal vein and capsule was not available in all the cases treated.)

Surgery			Surgery + R.		
Cases	3-Year Survival		Cases	3-Year Survival	
25	12	48%	97	44	45%
Vein positive 3/20 15%			Vein positive 32/77 42%		
Capsule positive 4/14 29%			Capsule positive 45/71 63%		

Pre-operative Irradiation

The aims of pre-operative irradiation are to shrink the primary tumour, reduce the reproductive integrity of its cells, destroy direct extensions, increase the mobility of a tethered organ, and eradicate limited metastases in regional nodes. As a result the operation should become easier with less risk of local recurrence and of distant metastases. Excision of the tumour finally removes residual radio-resistant elements. The general principles and prospects for pre-operative irradiation have been reviewed by Herbst, Cooley and Ozarda (1966), Cady (1968), and recently by Nickson and Glicksman (1972).

The theoretical advantages of pre-operative irradiation in clinical practice are supported by abundant radiobiological data including many animal experiments (see review by Powers and Palmer, 1968). In such studies, limited doses of irradiation make tumour cells less likely to become established and flourish after local implantation, or develop as metastases in distant organs following intravenous injection.

Some encouraging preliminary observations or results have been produced by pre-operative irradiation in patients with cancer at such sites as the head-and-neck, oesophagus, cervix, corpus

uteri and recto-sigmoid colon, and these have been achieved without a serious increase in post-operative morbidity or mortality, compared with surgery alone. In the sphere of urological cancer, pre-operative irradiation (4,000 rads in approximately 4 weeks) with subsequent cystectomy is being carried out in patients with locally advanced bladder cancer, in the hope of this being more effective than either radical radiotherapy or surgery separately (Whitmore *et al.*, 1968; Werf-Messing, 1971; Bloom, 1971*b*). Windeyer and Riches (1964) have described in detail the response of individual cases of renal cancer to pre-operative irradiation, and Flocks and Kadesky (1958) and also Flocks (1970) have referred to a small group of patients in which this treatment gave somewhat more favourable results than nephrectomy alone.

The overall time taken for a combined treatment programme involving pre-operative irradiation (*e.g.* 4,000 rads in 4 weeks) and subsequent surgery can be as long as 12 weeks (Bloom, 1971*b*). On the other hand, from radiobiological considerations, a dose of only 1,000 to 2,000 rads delivered over a few days immediately prior to operation, is considered by some authors also to be of value in reducing the risk of local recurrence and metastases (Berry, 1965; Werf-Messing, 1969). If this type of limited treatment with no interval to surgery is effective, it has the advantage of enabling the patient to have a quicker return to normal life and work. On the other hand, such low-dose irradiation may be insufficient, and the time-interval before operation too short, to permit a substantial decrease in tumour size. Furthermore, the gradual reduction of tumour during a more prolonged course of treatment lasting, say, 4 weeks is probably associated with improvement in local vascularity and tissue re-oxygenation, and this may favour radio-responsiveness in the remaining tumour fraction for which there is still treatment in hand.

Neither the delay in performing surgery nor the absence of histological confirmation before operation constitute strong arguments against pre-operative irradiation for renal cancer. An interval of approximately 4 weeks between irradiation and operation must represent, in most cases, only a small fraction of the total tumour time, and with modern radiological techniques (nephrotomography, arteriography) a firm pre-operative diagnosis can be made in over 95% of cases (Evans, 1968).

What action should be taken if, following pre-operative irradiation, subsequent laparotomy reveals a benign renal lesion? Fractionated irradiation to a total dose of 2,000-2,500 rads to the whole of one kidney is associated with impairment of renal function in man (Avioli *et al.*, 1963) and in experimental animals (Gup *et al.*, 1967). When such doses are given to both kidneys there is a substantial risk of dangerous late sequelae (Kunkler, Farr and Luxton, 1952). This risk varies from individual to individual and appears to be less if part of each kidney is shielded. When a non-malignant kidney has inadvertently received approximately 3,000 rads, a reasonable policy would be to postpone nephrectomy until there are signs of progressive renal impairment or hypertension which are unlikely to occur in all cases.

Pre-operative irradiation would appear to be a more rational approach to combined cancer therapy than postoperative treatment after the primary lesion has been removed. Co-operative clinical trials have now been set up in the United States, in London and in Rotterdam to determine whether pre-operative radiotherapy followed by nephrectomy is a better treatment for operable renal cancer than surgery alone. Preliminary results from the Rotterdam Radiotherapy Institute show a trend, not yet significant, in favour of the combined treatment (Werf-Messing, 1972). In this study the incidence of difficult and incomplete tumour removal is already significantly less following pre-operative irradiation than after immediate nephrectomy (Table VIII).

The Clinical Trials Committee of the Institute of Urology, London, has recently set up a co-operative controlled study involving several hospitals in the city to evaluate pre-operative irradiation in cases of operable renal carcinoma. The treatment protocol is shown in Figure 1. A similar co-operative trial has been developed in the United States (Nickson and Glicksman, 1972) following an encouraging pilot study in which pre-operative irradiation (3,000-5,000 rads in 4-5 weeks) was well tolerated: reduction in tumour size and vascularity was seen in 8 of 14 patients who had post-therapy arteriography, and no greater technical difficulty was experienced

with delayed nephrectomy compared with immediate operation (Lacy, Cox and Blake, 1967). The dose of pre-operative irradiation proposed for the American study is substantially higher (4,500 rads in 5 weeks) than that recommended in the Institute of Urology protocol.

It has been suggested that the concept of pre-operative irradiation represents one of the most promising contributions in recent years to the treatment of cancer. Clinical trials are in progress

Table VIII

Incidence of Inoperable Cases and Incomplete Nephrectomies

Primary tumour staged by surgical and pathological criteria according to the U.I.C.C. (1968) system.

P1 = Infiltration of renal parenchyma only.

P2 = Extension beyond kidney but veins and lymphatics free.

P3 = Vein or lymphatic involvement.

Stage	Pre-operative Irradiation + Operation	Operation
P1	0/16	0/17
P2	1/10	5/15
P3	6/26 (22%)	11/21 (52%)
Total	7/52 (14%)	16/53 (30%)

Werf-Messing (1972).

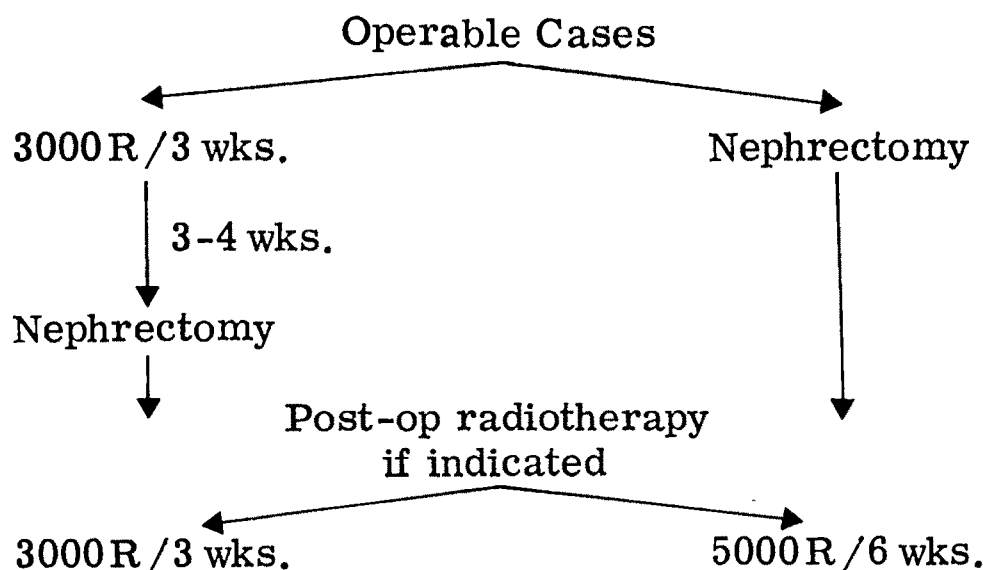


Fig. 1. Renal carcinoma trial, Institute of Urology, London.

to ascertain whether this applies to cancer of the kidney. Until these results become available, there is every reason to recommend pre-operative treatment for non-trial cases with particularly large or tethered tumours.

Risk of Treatment to Host Resistance?

In recent years many clinicians have become concerned with the possible deleterious effect of therapeutic endeavours on intrinsic defence mechanisms in patients with cancer. It is feared that

local irradiation, systemic chemotherapy or dissection of uninvolved regional lymph nodes may cause harm in early cancer cases by interfering with host resistance. So far, this concept has been applied principally to women with breast cancer, and has already encouraged a more conservative attitude towards the treatment of this disease (Crile, 1965, 1970; Bond, 1967). To some extent, a similar attitude may be developing in relation to renal carcinoma following the widely quoted report by Peeling *et al.* (1969), in which the results of nephrectomy and postoperative irradiation at the London Hospital were inferior to those of nephrectomy alone.

Clinical opinions regarding the possible harmful effects of radical treatment for cancer have been influenced by the results of animal experiments, mainly those reported by Crile (1965), in which tumour growth was accelerated by interfering with regional lymph nodes. The need to preserve such nodes intact for the benefit of the host is not supported by other laboratory studies, such as those of Gardner and Rosen (1967), Hammond and Rolley (1970), and Pilch, Bard and Ramming (1971).

The cells principally concerned with immune reactions, the lymphocytes, are extremely sensitive to irradiation. Prophylactic postoperative radiotherapy has been shown to cause a prolonged reduction of these cells in the peripheral blood of patients with breast cancer (Meyer, 1970; McCredie, Inch and Sutherland, 1972). The so-called "T" lymphocytes (of thymic origin), as opposed to the "B" lymphocytes (of marrow origin) are chiefly affected in this long-lasting lymphopenia (Stjernswärd *et al.*, 1972). The "T" lymphocytes appear to play a major role in cell-mediated immunity, and Stjernswärd *et al.* (1972) now raise the question as to whether this cellular change after irradiation is relevant to host resistance and to the development of distant metastases. On the other hand, McCredie *et al.* (1972) consider that, in spite of the resulting lymphopenia, the cellular immune response to cancer is unlikely to be impaired by local therapeutic irradiation.

Depression of immunological competence by treatment is not confined to radiotherapy, nor to chemotherapy, but may also occur following various standard surgical procedures (Riddle, 1967; Park *et al.*, 1971). This effect appears to be particularly marked in patients with heart disease or cancer (Park *et al.*, 1971), and may explain the sudden appearance of metastases during or soon after the postoperative period.

So far there is no convincing data in clinical practice that a significant reduction in host resistance to cancer, leading to an exacerbation of the disease, occurs following local therapeutic irradiation. On the contrary, modern megavoltage radiotherapy, sometimes involving extensive prophylactic lymph node irradiation, has greatly improved survival rates in cases of seminoma testis, carcinoma cervix, localised lymphoma and Wilms' tumour. Indeed, it is only since large-volume irradiation has been employed that substantial cure rates have been reported in, for example, Hodgkin's disease (Easson and Russell, 1963), and failure to cure seminoma has become a rarity (Smithers, Wallace and Wallace, 1971). We have shown that a combination of radical surgery and postoperative irradiation in women with early medullary breast cancer, a tumour believed to be associated with a strong host reaction, achieved a corrected 20-year survival rate of virtually 100% (Bloom, Richardson and Field, 1970).

From the available evidence regarding initial immunological reactions, local irradiation or surgical removal of regional lymph nodes in patients with well-established cancer is unlikely to interfere significantly with any host defence mechanism leading to accelerated tumour growth. Whilst events relating to the primary immune response to tumour antigens may be a local affair, by the time patients present with clinical cancer, any immunological reaction evoked in the host has almost certainly become generalised. Indeed, if such a response was ever present, it is likely to be on the decline or even completely exhausted due to increasing tumour activity at the time of clinical presentation.

Based on current immunological considerations, there is little at present to support a policy of less radical surgery or of avoiding radiotherapy in cases of renal cancer. Furthermore, the development of any possible immunological treatment for malignant disease is likely to be depen-

dent upon the initial eradication of as much tumour as possible by conventional methods, namely, surgery, chemotherapy and radiotherapy.

In the current prospective trials concerning the value of adjuvant radiotherapy for renal carcinoma (and indeed other tumours), the opportunity to study white blood cell changes and immunological reactions in irradiated and control cases should not be neglected.

Prospects for increasing Tumour Response to Irradiation

Oxygenation

Renal cell carcinoma is particularly prone to develop extensive areas of necrosis and haemorrhage in which poorly oxygenated but viable tumour cells are likely to be present. It is widely believed that the presence of such hypoxic cells in tumours is a major factor in those cancers which are not eradicated by irradiation. Many *in vivo* and *in vitro* experiments have shown that such cells can withstand doses 2 to 3 times greater than those which are lethal for fully oxygenated cells. The hypoxic elements remaining in a tumour following treatment may act as a focus for recurrence. This concept has led to various attempts to utilise the effect of oxygen in radiotherapy. The principal method, introduced some 15 years ago, aims to increase the oxygen content of the blood supply to tumours by making patients breathe oxygen in a hyperbaric chamber during irradiation (Churchill-Davidson, 1967). The initial technical difficulties of this approach have been largely overcome, and preliminary results from some current clinical trials give hope of achieving better local control of certain types of cancer (see reviews by Morris, 1972, and by Plenk, 1972). No attempt appears to have been made to use hyperbaric oxygen as an adjuvant during external beam therapy for renal cancer. If the results from various current clinical trials for tumours at a number of sites are sufficiently encouraging, this approach for carcinoma of the kidney would seem worth exploring.

Neutron Therapy

An alternative and perhaps ultimately more rewarding approach to the problem of tumour cell hypoxia is through the use of fast neutron beams which are less dependent than X or gamma rays upon the presence of oxygen for their biological effect (see review by Duncan, 1972). Fast neutrons are expected to produce greater damage to hypoxic cancer cells than photons but with no greater effect on adjacent well-oxygenated normal tissues. A neutron particle beam may, therefore, prove a more effective treatment against relatively radio-resistant tumours of which renal cancer is a good example. However, before this type of treatment can become more widely available for study much more fundamental work needs to be done, both with regard to the development of suitable apparatus for clinical use and the selection of dose-time factors which will achieve the optimum biological effect.

Machines for neutron therapy are now available in several American and European Centres from where preliminary observations are awaited with considerable interest. Such machines, however, are bulky and very expensive to build and maintain. A more compact unit (deuterium-tritium generator) producing 14 MeV neutrons has been specially developed for clinical use in England, and has recently been installed for pilot studies in centres in Manchester and Glasgow. On theoretical grounds, fast neutron therapy appears to present a promising new technical development towards the control of the more radio-resistant types of cancer, with the promise of being approximately 1.5 times more effective than super-voltage X-rays. This assumes that radio-resistance in such cases is largely due to tumour hypoxia, but factors other than oxygen may be involved in this problem which call for alternative lines of research.

Radio-sensitisers

Other efforts to improve radiotherapy results have been directed to finding chemical agents with which it is hoped to enhance the effect of irradiation. For example, there is experimental evidence

that actinomycin D and certain pyrimidine analogues (*e.g.* 5-bromo-2-deoxyuridine) have this property. Clinical experience in this field, however, has been disappointing, and it would therefore seem premature to progress from pilot studies to prospective trials, using chemicals as sensitising agents, until more promising compounds have been discovered. Several groups are exploring this area of research, and we are at present investigating compounds of possible value, using the transplanted oestrogen-induced renal cell tumour of the Syrian hamster as an experimental model.

Cytotoxic Drugs

Adjuvant therapy with cytotoxic drugs may be used in cases of renal cancer to try and prevent the growth of malignant cells disseminated during nephrectomy (Gazet and Phillips, 1968). Such agents may also be administered in conjunction with postoperative irradiation to increase the destruction of residual tumour, or after surgery and irradiation as long-term intermittent chemotherapy with the aim of preventing or delaying the development of distant metastases.

Objective responses of renal carcinoma to a variety of cytotoxic agents have occasionally been reported, but any improvement has invariably been limited and of brief duration. Unfortunately, no useful compound against this disease has been discovered. Woodruff *et al.* (1967) reviewed some 60 reports in the literature concerning 33 different cytotoxic drugs for which the overall objective response rate among 243 cases was only 10%. In a personal series, Talley *et al.* (1969) obtained objective improvement in only 3% of 57 cases treated intensively with various preparations (Table IX). At the Memorial Hospital, New York, numerous chemotherapeutic agents, singly or in combination, were tried in 54 patients with metastatic renal carcinoma, but no objective responses were observed (Grabstald, 1964).

Table IX

Response of Advanced Renal Cancer to Cytotoxic Drugs

Author	Cases	Objective Response	
Woodruff <i>et al.</i> (1967)	243*	25	10.3%
Talley <i>et al.</i> (1969)	57	2	3.5%
Grabstald (1964)	54	0	0%
Total	354	27	7.6%

* Collected cases from 60 reports.

Fox (1965), using considerably larger doses of cyclophosphamide than are generally recommended (up to 50 g in 1 course), obtained useful palliation in some cases of urinary tract tumours, including 3 of 6 patients with renal carcinoma, in 2 of which marked objective regression was seen. On the other hand, Leiter, Edelman and Brendler (1966) found that even high local concentration of such drugs as 5-fluorouracil or methotrexate, achieved by continuous arterial perfusion of the kidney prior to nephrectomy, failed to produce any discernible changes in the operative specimen that could be attributed to the agent used.

Until a more effective and more selective cytotoxic agent is found against renal cell carcinoma, there can be little enthusiasm for setting up co-operative randomised trials designed to determine the value of adjuvant chemotherapy for this disease.

As a result of experience with lymphoma in adults and acute leukaemia and solid tumours in children, interest has now focused on the use of long-term, continuous or intermittent multiple

drug regimes in the wider management of advanced malignant disease. We have recently adopted this principle in our urological unit for advanced tumours, including metastatic renal cancer, using a combination of cyclophosphamide, vincristine, 5-fluorouracil and methotrexate (with folinic acid rescue) by intravenous drip at 4-week intervals, based on the method described at this hospital by Price and Goldie (1971).

Hormone Therapy

Many clinical observations suggest that renal cell carcinoma is a good example of human malignant disease which does not behave in an entirely autonomous fashion. The late appearance and slow growth of some metastases, the occasional cure following removal of a solitary deposit, and those rare examples of spontaneous regression of advanced tumours, all support the concept of natural control of the disease in some patients, at least for a time.

There is evidence that the controlling factors in renal tumours may be related to the endocrine system. Adenomas and adenocarcinomas of the kidney are found more frequently in men than in women. The majority of examples of spontaneous regression are found in males. In the experimental field, the influence of sex hormones on normal renal tissue and the production of renal cortical tumours in male hamsters by oestrogen, together with their inhibition by oestrogen-antagonists (Horning, 1956; Kirkman, 1959; Bloom *et al.*, 1967*a*) and castration (Bloom *et al.*, 1963*b*), support the idea of hormone-dependency in renal cell tumours.

Caution is, of course, necessary when trying to extrapolate from observations in laboratory animals to clinical practice, but because the principle actions of hormonal agents are fundamentally alike in most species, it is tempting to apply knowledge derived from endocrine-dependent tumours in animals to possible analogous tumours in man. The relationship between human renal cancer and the endocrine system is strengthened by the hormone secretion (erythropoietin, parathormone-like substance) of some renal tumours and their metastases.

Encouraged by this background, we started to use sex hormones for patients with far advanced renal cancer (Bloom, 1964; Bloom and Wallace, 1964). Our 10-year experience with this treatment in 80 patients with incurable renal carcinoma has recently been reported (Bloom, 1971*a*). It is hoped that information gleaned from such observations may be helpful in indicating a possible adjuvant role for hormones in less advanced cases.

Only patients with clear evidence of advancing disease were accepted for this study. No case was refused treatment, no matter how near death appeared to be. Thus 20 very ill patients died within 6 weeks of commencing hormone therapy, that is 25% of the total series. Treatment in all cases was started with a progestin, Provera in 79 cases, and Delalutin in 1 case. Provera was administered orally in a dose of 100 mg t.i.d. If the progestin failed, it was replaced by testosterone propionate, 100 mg intramuscularly, 3 to 5 times a week.

Some degree of subjective benefit was experienced by 44 patients (55%). There were 11 cases (14%) in which undeniable improvement in the radiological or clinical signs of tumour occurred within a short time of commencing treatment, or changing to a different hormone. In 2 additional cases there was marked improvement in general condition associated with stationary tumour for over 20 months. A definite objective response was therefore observed in 16.5% of the total series for periods ranging up to 3 years (Table X; for illustrative cases see Bloom, 1971*a* and 1972). In a further 10 cases minor, transient or doubtful objective improvement was recorded, but these will not be considered further.

Hormonal-response Interval

The time between commencing or changing a hormone preparation and observing signs of clinical improvement in the 11 cases with definite tumour regression was remarkably short, varying from 2 to 6 weeks. Patients may feel and look better within a week or 10 days of starting

treatment. Other authors have reported examples of regression only after 2 or more months of continued treatment (Samuels, Sullivan and Howe, 1968; Talley *et al.*, 1969).

Table X

Advanced Renal Adenocarcinoma: Results of Hormone Treatment—80 Cases (Bloom, 1972a)

Response	Cases	
Subjective	44	55%
Objective		
Marked tumour regression	11*	14%
Tumour stationary > 1 year	2†	2.5%
Slight tumour regression	10	12%
Total Objective	23	29%

* For 2, 2, 3, 3, 3, 9, 13, 20, 24, 24, 35 months.

† For 21, 20+ months.

Duration of Life in Hormone-treated Cases

Clinical improvement in patients with renal carcinoma during hormone therapy appears to be associated with prolongation of life (Table XI). Of 11 patients who died after showing a definite

Table XI

Average Survival of Patients with Advanced Renal Carcinoma Treated by Hormones

Objective Response	Cases	Average Survival (months)
Present	11*	19.6
Absent	67	5.2
Total	78	7.2

* Excluding 1 untraced case and 1 still alive.

objective response, the average survival was 19.6 months, compared with only 5.2 months in 67 cases who failed to respond favourably.

Influence of Sex on Hormone Response

Marked objective improvement occurred more often in men (11 of 54 cases, 20%) than in women (2 of 26 cases, 8%). In this series and in most others, the best results, including the disappearance of tumour, have been confined to men. However, good objective responses in women have been reported by Samuels *et al.* (1968) and also by Wagle and Murphy (1971).

Other Reported Series

Since our first communications (Bloom *et al.*, 1963a; Bloom, 1964) there have been 8 reports from other centres concerning the hormone treatment of advanced renal cancer (Table XII). The overall picture is 1 of 5 or 6 cases responding to this treatment. Of a total of 228 collected

cases, 17% showed an objective response, chiefly to progestins. A rather more optimistic result is obtained when selected case-groups are examined (Table XIII). For example, in the present series, by excluding patients who died within 6 weeks of commencing treatment, the overall objective response rate increases to 22%, whilst in males it reaches 27%.

Table XII

Advanced Renal Adenocarcinoma treated with Progestins/Androgens:
Reported Results

Author	Hormones Used	Cases	Objective Response	Successful Hormone	
				P	A
Woodruff <i>et al.</i> (1967)	P	4	1 (25%)	1	—
Melander <i>et al.</i> (1967)	P + A	20	4 (20%)	P + A 4	
Jenkin (1967)	A	15	1 (7%)	—	1
Samuels <i>et al.</i> (1968)	P/A*	23	4 (17%)	3	1
Talley <i>et al.</i> (1969)	P/A	16	2 (12%)	2	—
Papac (1969)	P/A*	12	4 (33%)	0	4
Paine <i>et al.</i> (1970)	P	15	3 (20%)	3	—
Wagle and Murphy (1971)	P/A*	43	8 (17%)	6	2
Bloom (1971)	P/A*	80	13 (16%)	12	1
Total		228	40 (17%)		

P = Progestin.

A = Androgen.

* = Androgen generally used for progestin failures.

Table XIII

Advanced Renal Adenocarcinoma: Hormone Response in Selected Groups

Author	Group	Response	
Melander <i>et al.</i> (1967)	T + P for at least 12 weeks	4/13	31%
Paine <i>et al.</i> (1970)	P in males	3/12	25%
Bloom (1971)	Excluding deaths < 6 weeks	13/60	22%
	Males, excluding deaths < 6 weeks	11/41	27%

P = Progestins.

T = Testosterone.

Spontaneous Regression of Renal Carcinoma

The obvious question now is whether the regression of metastases reported in hormone-treated cases is the result of such treatment or due to an unrelated spontaneous change. Spontaneous partial or complete regression of renal cancer is a well-recognised but rare event (Everson and Cole, 1966). In a personal series of some 200 cases of renal carcinoma referred for radiotherapy or hormone treatment, I have seen only 2 examples of spontaneous regression. In 1, a woman of 70, reduction of pulmonary metastases occurred for only 3 months, during which time the

patient's general condition deteriorated, mediastinal nodes increased, and vaginal metastases appeared (Bloom, 1967a). The second case was far more impressive:

A nephrectomy for renal carcinoma was performed on a man aged 55 (Case No. 077552). Multiple bilateral pulmonary metastases were present at the time of nephrectomy. Postoperatively, he was referred for hormone treatment, but in keeping with our "wait and see" policy in such cases, no hormone treatment was undertaken until there was clear evidence of tumour progression. 2 months later some metastases were smaller, and by 7 months all but one had disappeared. 10 months after nephrectomy the lungs were clear. The patient remains in excellent health with a clear chest, 4 years after operation (Bloom and Riddle, 1973).

In view of the rarity of spontaneous improvement in metastatic renal carcinoma, it appears that definite regression lasting from 2 months to nearly 3 years in 11 cases, continued tumour standstill for over 20 months in 2 others (bone and lymph node metastases), and minor or doubtful changes in an additional 10 (not considered further), in a consecutive series of 80 cases receiving hormone therapy, is more likely to be due to this treatment and not the result of an unrelated natural event. This concept is strongly supported by the extremely short interval between starting or changing hormone treatment and observing clinical or radiological signs of improvement, and also by reports of similar experience from 8 other centres (Table XII).

Selection of Cases and Hormonal Preparations for Treatment

Hormone treatment is contra-indicated in patients with strictly limited metastases which are suitable for a local and more radical, perhaps curative, procedure such as excision of solitary pulmonary or cerebral deposits. Although a good objective response to hormone therapy may be a more dramatic event than a response to irradiation, the latter is far more often successful in relieving symptoms, particularly bone pain, than treatment with cytotoxic or hormonal agents.

In primary cases of endometrial cancer the administration of progestins as adjuvants prior to irradiation or surgery may give better results than immediate conventional treatment (Sherman, 1966; Bönke, Decoster and Ide, 1970). On the other hand, no clear advantage has been established for prophylactic hormone treatment for breast cancer. Our experience with hormone treatment for renal carcinoma has, so far, been confined to advanced cases. It remains to be seen whether hormone therapy has a place as an adjuvant in the management of earlier cases. An important factor in this context is the possible enhancement of tumour growth which may occur in some hormone-treated cases, although such an event appears to be rare in renal cancer (Bloom, 1972).

In vitro observations in this Institute, using organ culture techniques, indicate that hormones probably act directly on human renal tumour cells and spare normal kidney tissue (Tchao *et al.*, 1968), an apparently ideal situation for the systemic treatment of cancer. By means of tissue culture and also tumour-transplants in immunosuppressed laboratory animals, it is hoped to determine the hormone-dependency of a particular patient's tumour, and the agent most likely to be effective against it. However, a close correlation between such laboratory studies and clinical experience has yet to be established.

Immunotherapy

In recent years there has been an explosive revival of interest in the immunobiology of cancer, but in spite of mounting evidence for tumour-associated antigens in human malignant disease capable of evoking a host reaction, therapeutic endeavours in this field have met with little success in terms of tumour regression or increased patient survival (see reviews by Fairley, 1969; Sophocles and Nadler, 1971; Anderson, 1972; Currie, 1972).

Renal tumours have been readily induced in laboratory animals by a variety of chemical, physical, hormonal and viral agents. A search has been made among such observations for possible clues to the aetiology of human renal cancer (Dukes, 1961; Bloom, 1967b). The likelihood of extrinsic carcinogens being responsible for at least some tumours of the kidney was considered to increase the possibility of finding tumour-associated antigens in this disease. A

number of laboratory studies suggest that such antigens may indeed be present in cases of renal carcinoma. Thus, the formation of a weak precipitin against this tumour was provoked in a patient by Nairn *et al.* (1963) by injecting similar tumour material from another case, but this had no influence on the course of the disease.

Evidence for tumour-specific cell-mediated reactions in patients with renal cancer is to be found in several *in vitro* studies. Thus, Stjernswärd *et al.* (1970) showed that the patients' own lymphocytes were stimulated to increased DNA synthesis by autologous tumour cells, but not by autologous non-malignant cells. Hellström *et al.* (1971) and also Bubenik *et al.* (1971) demonstrated that leucocytes from cases of renal cancer could be cytotoxic for autologous tumour cells.

Although the principal mechanism for tumour rejection is through activated lymphoid cells, non-cellular factors may also be involved in the defence mechanism against cancer. Humoral antibodies against renal carcinoma cells have been demonstrated by Ravitz, Watne and Milam (1972) using immunofluorescent techniques. Shore *et al.* (1970) have shown that the addition of patients' serum to the medium in which autologous or homologous renal carcinoma cells are growing in monolayer culture caused their total destruction within 72 hours, whereas control sera from normal people and patients with other tumours rarely had this effect.

On the clinical and more practical side, examples of occult tumour, long-standing stationary tumour, delayed recurrence, spontaneous regression, and failure of circulating cancer cells to become established in patients with renal cancer, all suggest the existence of some degree of natural tumour control. This may be the result of hormonal influences, as suggested by the tumour response in some advanced cases to progestins or testosterone, or to immunological mechanisms: perhaps both are involved.

An immunological approach to the treatment of patients with renal cancer is exciting and could be rewarding but, so far, apart possibly from acute leukaemia (Mathé, 1970), such attempts have failed to control human malignant disease. These have included the administration of irradiated autologous tumour cells with or without Freund's adjuvant, non-specific agents such as B.C.G. or C. Parvum, convalescent serum from cured cancer patients, and sensitised lymphocytes from donor patients or normal individuals.

Dr Graham Currie of the Institute of Cancer Research (personal communication) has found evidence for a defence reaction to tumour-associated antigens in cases of renal carcinoma, using a microculture technique to assess cytotoxicity of host lymphocytes. This reaction was related to the clinical extent of the disease. Thus, lymphocytes from patients with non-metastatic carcinoma reacted against autologous tumour in tissue culture, whereas this cellular reaction was often absent with material from cases with distant metastases. Currie has also shown that *in vitro* tumour cell lymphocyte interactions can be evoked or enhanced in patients with renal cancer by specific active immunisation with autologous tumour cells.

Whilst many research groups are striving to develop methods of immunotherapy against cancer, it is generally agreed that such an approach at the present time, no matter how promising, would have to be combined with conventional treatment, first aimed at destroying or removing as much tumour as possible. It seems that immunotherapy can only be successful if a relatively small number of residual cancer cells have to be eliminated. Thus, following nephrectomy and radiotherapy to the renal bed and para-aortic nodes, specific active immunotherapy using a vaccine prepared from the patient's own irradiated tumour or, alternatively, specific adoptive immunotherapy with sensitised lymphocytes, may prove more effective in destroying residual malignant cells than irradiation alone. Cohen and Cohen (1956) and also Haddow and Alexander (1964) reported an increased response to irradiation of experimental tumours following injections of irradiated tumour autograft. This might be explained by the destruction, through immunological mechanisms, of residual cells after eradication of the main tumour mass by conventional treatment.

Finally, attention should be drawn to the possible dangers which may be associated with attempts at immunotherapy, particularly tumour enhancement (Koldovsky, 1966; Prehn, 1972).

So far, these are largely theoretical, but in a randomised co-operative clinical trial at the Royal Marsden Hospital and St George's Hospital, London, it was disturbing to find that the survival rate of patients with cerebral glioblastomata, treated by surgery and postoperative radiotherapy combined with specific active immunotherapy (injections of irradiated autologous tumour cells), was lower than in control cases treated by surgery and radiotherapy (Bloom *et al.*, 1973).

To summarise: the ultimate aim of immunological research is to identify and exploit any tendency to a host response against a tumour in order to eradicate residual disease *after* maximal conventional treatment (surgery, radiotherapy and chemotherapy). In this sense immunotherapy can only be adjunctive to standard methods of treatment. Investigators in this field must be ever alert to possible harmful effects of such treatment due to interference with natural host defence mechanisms.

Conclusions

Efforts to find useful adjuvant therapy for renal carcinoma along the various lines indicated should not be restricted to advanced cases: late cases can give only poor results. Attempts should be made to apply the maximum therapeutic effort to earlier cases, but here one must be ever watchful for possible serious side-effects, be they irradiation damage, toxicity from drugs, or perhaps a significant depression of host defence mechanisms. The best treatment for renal carcinoma may emerge only after the results of properly conducted clinical trials have become available. Opinions based solely on retrospective studies can be misleading, especially if no account is taken of tumour extent (Petkovic, 1959; Whitmore and Krause, 1967), nor of histological grade (Myers *et al.*, 1968). Even in controlled trials investigators are not absolved from considering such important and well-established prognostic factors. Thus, in spite of randomisation and careful staging, the composition of certain case-groups in cancer series may still be biased by the vagaries of chance to contain more intrinsically favourable or unfavourable tumours, and this may give misleading results (Bloom, 1971c).

What policies should be adopted by urologists and radiotherapists in the treatment of renal cell cancer?

1. First, they should work together, preferably in joint consultation clinics, to try and determine the most effective means of treating the disease according to certain well-established variables.
2. They should enlist the co-operation of pathologists and call for a generally accepted classification of the disease without which the accurate assessment of treatment results is not possible. In the meantime they should fully record the clinical, surgical and pathological data concerning each of their own cases.
3. They should set up clinical trials or join existing ones to evaluate pre-operative radiotherapy in operable cases.
4. When faced with large tethered tumours, pre-operative irradiation should be given, after which operability is re-assessed.
5. In the presence of gross or suspected residual disease after nephrectomy, postoperative irradiation would seem warranted.
6. Clinical trials should be set up to evaluate long-term prophylactic hormone treatment.
7. The search for more useful cytotoxic agents should be made in association with chemotherapists and experimentalists interested in this field of investigation. Pilot studies in advanced cases should be undertaken to assess the value of multiple drug regimes. Agents of promise should then be submitted to co-operative clinical trials involving patients with operable tumours.
8. Further fundamental research is required before clinical trials are launched to explore the possible value of immunotherapy following conventional radical treatment.

Although "best cases" which have a 5-year survival rate of 90% should be treated by nephrectomy alone, their immune capabilities should be studied by appropriately trained workers since

it is in these fortunate patients that the basis of an effective host resistance against renal cancer may be found.

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The Value of Radiotherapy in the Treatment of Hypernephroma—a Clinical Trial

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The radical treatment of hypernephroma or renal cell carcinoma has been accepted as primarily, if not solely, a surgical problem. Riches (1964) states “whatever ancillary methods are employed the only effective treatment of malignant renal tumours is a surgical removal. In almost every case this implies nephrectomy.” This approach is similar to that expressed by Paterson in his book (1963), where these tumours are classified under the heading of “Radiotherapy Usually Contra-indicated” and qualified by the statement “in this group surgical excision must be selected as the treatment of choice and must expect no help as a curative measure from radiotherapy as a pre- or post-operative procedure”. This basic policy is based on a number of factors. Firstly, and of primary importance, is the relative non-responsiveness of these tumours to irradiation. Accepting that radio-sensitivity and radio-resistance are relative terms, the dose of irradiation which needs to be given to eradicate renal cell tumours is of such magnitude that the tolerance of the normal tissues is far exceeded. This poor responsiveness to irradiation is further accentuated by the macroscopic features of many of these tumours which often contain areas of necrosis with associated avascularity and blood cystic spaces; features which would further lessen the responsiveness of the tumour to ionising irradiation in view of the anoxic tissues present. Further features which suggest that radiotherapy is unlikely to play anything more than a minor part in the treatment of these malignant tumours is the natural history of the lesions with a propensity to invade veins and hence disseminate widely and finally the complementary factor of the large volume of tissue to be irradiated in order to encompass all sites of possible local extension, specifically including the renal bed, para-aortic gland area and surgical scar. Not surprisingly, therefore, the survival rates for renal cell tumours treated by surgery have shown very little improvement over the years with 5-year survival rates in different published series varying from 33%–48% (Table I). Three series of cases of hypernephroma have, however, been published in which an attempt was made to improve the results of treatment by the addition of postoperative radiotherapy. Riches, Griffiths and Thackray in 1951, Flocks and Kadesky in 1958 and Bratherton in 1964 showed in their respective series that postoperative irradiation did increase the survival rates at the 5- and 10-year periods (Tables II, III and IV).

In each of the series definite improvement was noted in survival rates even though the series were not randomised trials. In view, therefore, of these published figures and the noted improvement it was felt that a randomised trial should be undertaken to evaluate the place of radiotherapy given postoperatively on a more accurate basis. This paper is a review and an analysis of the results from this trial undertaken by the combined Urological and Radiotherapy Units at the Newcastle General Hospital from 1961 to 1970. No absolute results can be given at the present time and the presentation can be regarded only as an interim report as many of the cases were treated too recently to give any true absolute results.

Patients and Methods

The criteria for acceptance in the Trial were histologically proven cases of renal cell carcinoma in which there was no macroscopic malignancy remaining after operation and with no metastases

demonstrable either clinically or on X-ray of the chest and the part of the spine included in the pyelograms. The primary tumour was to be removed completely by nephrectomy and the supra-renal gland where necessary, together with any obviously enlarged metastatic nodes, but no attempt was made at any form of so-called radical para-aortic node dissection.

After the nephrectomy each acceptable case was allocated to one of two groups depending on whether his birthday was on an odd or an even date. In one group no further treatment was given; in the other each patient was given a postoperative course of radiotherapy by a standard treatment regime. The volume of tissue to be irradiated in order to include the renal bed, incision

Table I
Renal Cell Carcinoma—Crude Survival

	3 Years	5 Years	10 Years
	%	%	%
Priestley (1939)	48	38	27
B.A.U.S. (1951)	45	33	18
Mostofi (1961)	56	48	22

Table II
B.A.U.S. Series (Riches, 1951)

Years	Surgery Only (685)	Surgery + Radiotherapy (131)
	%	%
1	80	86
3	44	53
5	30	49
10	17	27

Table III
Survival—353 cases
(Flocks and Kadesky, 1958)

Years	Surgery Alone	Surgery + Radiotherapy
	%	%
5	48.2	52.5
10	46.0	55.0

Table IV
Radiotherapy and Renal Cell Carcinoma—
125 Cases (Bratherton, 1964)

Years	Surgery Alone	Surgery + Radiotherapy
	%	%
1	64	59
3	38	44
5	29	43
10	27	33

area and para-aortic node sites was achieved by extending the fields 1.5 cm over the midline between the 11th dorsal and 3rd lumbar vertebrae and incorporating the surgical scar. The dimensions of the fields were adjusted according to the size of the patient and the size of the original tumour mass.

105 cases were originally included in this Trial, but 5 of these cases were subsequently excluded as not fitting the requirements of the protocol. In these 5 cases there was suspicious but not proven evidence of metastases at the time of the surgical procedure which subsequently turned out to be definite metastases and hence were removed from the Trial. Of the 100 cases remaining, 51 were treated by combined surgery and postoperative irradiation and the remaining 49 by surgery only. These cases are now presented for review and analysis.

Results

Crude Survival

Analysis of survival ranging from a minimum of 2 years to a maximum of 11 years from the time of the initial surgical procedure showed that 28 cases treated by surgery only have survived as compared with 21 who had surgery plus radiotherapy. These cases include patients who had survived but had evidence of recurrence, numbering 3 in the surgery-only group and 6 in the combined radiotherapy/surgical group. The differences are, therefore, even more marked when the survival disease-free rate is noted, being 25 and 15 respectively (Table V). These results are further analysed according to the numbers at risk at the first, third and fifth postoperative years and shown in Tables VI and VII. Whilst the 5-year survival varies between 36% in those cases treated with additional radiotherapy and 44% in those cases treated by surgery only, an even greater difference is noted at the end of the first postoperative year when the differences are

Table V
Crude Survival Time

	Alive and Well	Recurrent	Dead
With radiotherapy	15	6	30
Without radiotherapy	25	3	21

Table VI
With Radiotherapy—51 Cases

Years at Risk	Numbers	Alive	Percentage Alive
1	51	37	72
3	41	25	61
5	30	11	36

Table VII
Without Radiotherapy—49 Cases

Years at Risk	Numbers	Alive	Percentage Alive
1	49	41	83
3	38	25	66
5	27	12	44

72% and 83% respectively. However, none of these differences is significant statistically even where the recurrent disease is excluded from the crude survival rate. The immediate observation from these survival figures is that the group of cases treated by combined surgery and post-operative radiotherapy reveal a trend to do rather worse than those treated by surgery only. As radiotherapy has been prescribed with the object of eradicating or reducing recurrence of the tumour following surgery in either the tumour bed, scar or local node areas, the effectivity of this added modality was assessed. This analysis is shown in Table VIII where division was made into 3 main groups to estimate this incidence of local recurrence as well as for generalised metastases and coincidental cause of death.

1. The incidence of generalised metastases is seen to be very little different between the 2 groups, 14 cases in the radiotherapy section showing evidence of disseminated metastases at death as compared with 16 in the surgical only group. In 4 cases in the latter group there was evidence of both local recurrence and generalised metastases. It can be suggested therefore, that in many of these cases dissemination had occurred before or during the surgical procedure so that postoperative radiotherapy would be unlikely to affect the survival.

2. The incidence of recurrence occurring "locally" in either the tumour bed or scar or regional node areas is also almost identical between the 2 series, occurring in 8 cases, including 3 cases who are still alive but recurrent in the radiotherapy group compared with 9 cases, including 1 case alive and recurrent in those cases treated by surgery only.

In the coincidental cause of death the mortality is noted to be very much higher in the radiotherapy section as compared with the other. The causes of death included 3 cases of cardiac failure, 2 cases of other malignancy, 1 case of suicide and 4 cases labelled "liver failure". It is with particular interest that the cases labelled "liver failure" are noted; these will be discussed in greater detail later in the paper.

Table VIII

Cause of Death with Sites of Malignancy

With Radiotherapy		Without Radiotherapy	
Blood stream	14	Blood stream	16
Renal bed	5 (3)	Renal bed	8 (1)
Coincidental	10	Coincidental	2

Figures in brackets indicate cases still alive but recurrent.

Table IX

Time of Death

With Radiotherapy		Without Radiotherapy	
Years	Number	Years	Number
0-1	14	0-1	7
1-2	5	1-2	6
2-3	1	2-3	3
3-4	6	3-4	—
4-5	3	4-5	4
5+	1	5+	1
Coincidental	8	Coincidental	2

To summarise, therefore, radiotherapy does not appear to influence the incidence of generalised or blood-stream metastases or the incidence of local recurrence in the renal bed, scar or lymph node areas. There does result a far higher incidence of coincidental cause of death of which liver damage leading to liver failure appears to be directly attributable to the radiotherapy given.

Time of Death

The greatest differences between the 2 groups relating to the time of death were noted during the first postoperative 12 months. By the time of the first anniversary, reference to Table IX shows that in the section treated with additional radiotherapy 14 cases had died as compared with 7 cases in those treated by surgery only. Further analysis from the first to the fifth postoperative years showed that in the cases treated with additional radiotherapy 16 cases died as compared with 14 in the surgical group—almost equal numbers.

Factors influencing Prognosis

These various factors have been surveyed with particular reference to the criteria which in previous series have been accepted as applicable specifically to renal cell tumours.

1. Involvement of renal vein.
2. Extra-renal extension with capsular involvement.
3. Lymphatic extension.
4. Histological grade.
5. Size and weight of tumour.

Table X

B.A.U.S. Series (Riches, 1951)

Years	Surgery Only		Surgery + Radiotherapy	
	Vein Positive (166)	Vein Negative (519)	Vein Positive (33)	Vein Negative (98)
	%	%	%	%
1	61	83	78	88
3	28	49	44	55
5	16	35	36	50
10	6	21	25	27

Table XI

Relation of Results to Vein Involvement

	Number	Alive	Recurrent	Dead
Vein involved	32	10	3	19
Vein not involved	40	25	1	14

Vein Involvement

Previous series consider that this is undoubtedly the major factor which influences the prognosis. Riches considered that cases demonstrating venous involvement were helped by postoperative irradiation (Table X). In this series the vein was reported as involved in 32 cases and in 40 further cases the records specifically state that there was no evidence of vein involvement in the sections examined. In the remaining 28 cases no mention was made of this factor. The influence of vein involvement on prognosis is shown in Table XI, where it is noted that of the 23 cases with vein involvement 10 cases or 30% are alive and recurrence free as compared with 40 cases in which venous involvement is absent when 25 or 60% of cases are live and recurrence free. In order to try and assess the value of radiotherapy in those cases with vein involvement these results were broken down further although the numbers are too small to be of any statistical value. Table XII shows that in those cases given radiotherapy with positive evidence of venous invasion, 4 cases are alive and 13 are dead, or alive with evidence of recurrence. This compares with those cases

also with venous involvement which were treated by surgery only when 6 cases were noted to be alive and 9 either dead, or alive and recurrent.

To summarise, in the presence of venous involvement the prognosis in agreement with other series is poor, with proportionately twice as many cases being dead than alive without any obvious benefit from the addition of radiotherapy.

Capsular Spread

Noted spread to or through the capsule was confirmed histologically in 22 cases. The results reveal no improvement by the addition of radiotherapy in a very small number of cases but in the group treated by supplementary irradiation more cases are seen to be dead than alive as contrasted with the surgery-only section (Table XIII).

Lymph Node Involvement

The presence of histologically confirmed lymph node metastases was reported but rarely in this series, only 6 cases being confirmed, of whom 5 had already died. Three of these cases died within the first year after treatment due to recurrent malignancy, but the 2 other cases died without evidence of malignancy at the time of death, 1 case dying at 4½ years from cardiac dysfunction and the other case dying at 3½ years as a result of suicide. The patient who is alive was treated by surgery only and is clinically disease-free at 4 years.

Grade of Tumour

Attempts have been made previously to grade tumour and to correlate the resultant grade with prognosis. In this series the characteristics suggested by Thackray (1964) have been applied, grading the tumours according to Grade I—being the least malignant, Grade II—being intermediate and Grade III—the most malignant. 45 cases have been graded according to these criteria by one senior histologist (Table XIV).

37 cases have been graded as I,

8 cases have been graded as II and strangely

0 cases have been allocated to grade III.

The relationship of grade to prognosis is also shown. It is noted that in the 37 grade I cases 20 have died at an average time of 26 months after completion of treatment. This compares with the 8 cases in the grade II group, of whom 6 have died at an average time of 20 months following treatment. These results suggest that the grade II tumours are indeed more malignant and have a worse prognosis than the grade I.

Size of Tumour

The influence of the size of tumour on prognosis was attempted by reference to the macroscopic pathological report on the surgical specimen. Three arbitrary sizes were accepted, small, medium and large (1-5, 6-9 and 10+ cm in diameter respectively) and the influence of supplementary radiotherapy was noted (Table XV). It is difficult, if not impossible, to reach any conclusion relating to the various sizes of tumour and the influence of radiotherapy except to say that in all the subgroups those treated by surgery only appeared to have an appreciably better survival rate.

Effect on Liver Function

In this series it has been noted that the cause of death in 4 cases has been attributable to "liver failure". All 4 cases died within 5 months of completion of therapy. All 4 cases were right-sided lesions with a large volume of the liver included in the irradiated volume. Further cases have shown evidence of liver damage but with ultimate recovery. One of the latter provides greater details of the effect of irradiation on the liver.

Table XII
Effect of Irradiation on Venous Involvement

		Alive	Recurrent	Dead
Vein positive	With radiotherapy 17	4	2	11
	Without radiotherapy 15	6	1	8
Vein negative	With radiotherapy 14	8	1	5
	Without radiotherapy 26	17	0	9

Table XIII
Capsular Involvement

	Alive	Dead
With radiotherapy	2	8
Without radiotherapy	6	6

Table XIV
Renal Cell Carcinoma—Grade of Tumour
and Survival

Grade	No.	Alive	Dead	Time of Death (in months)
1	37	17	20	26
2	8	2	6	20
3	0	0	0	0

Table XV
Relationship of Size of Result

Size (cm)	Total		Alive	Dead
1-5	27	With radiotherapy 16	3	13
		Without radiotherapy 11	7	4
6-9	42	With radiotherapy 19	19	9
		Without radiotherapy 23	14	9
10+	31	With radiotherapy 17	8	9
		Without radiotherapy 14	9	5

Case Report 1

During the course of radiotherapy the patient sustained no undue radiation upset and completed the prescribed course of irradiation with no difficulty. Following completion of the radiotherapy he complained of increasing nausea, flatulent dyspepsia and vomiting accompanied by epigastric discomfort and distension. His condition deteriorated—he felt weak and generally off colour. Liver function tests revealed abnormalities suggestive of hepatocellular damage with raised serum alkaline phosphatase and serum bilirubin the main changes. Two years after

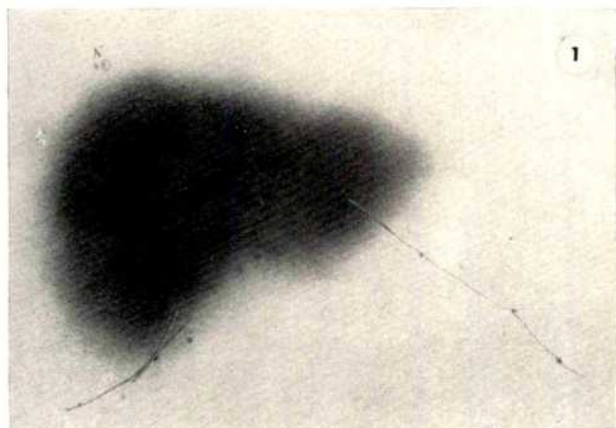


Fig. 1. Scan of normal liver.

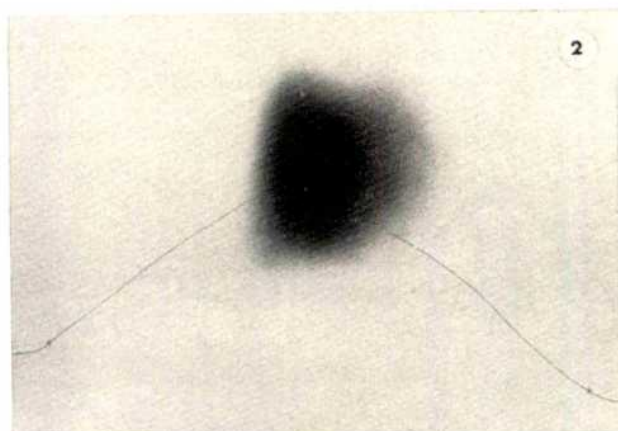


Fig. 2. Scan of liver 1 month after completion of radiotherapy showing absence of function, right lobe sharply demarcated.

completion of therapy his alkaline phosphatase still remains elevated and the thymol turbidity test has occasionally fluctuated above normal during the intervening months. Symptomatically gradual improvement occurred, with nausea, flatulent dyspepsia and a tendency to vomiting remaining for about 3 months. The amount of food taken at one meal was reduced and remains so. Epigastric discomfort cleared after 6 months but a palpable mass has been noted in the epigastrium for 12 months. Liver scans have demonstrated the following features during this period:

1. Absence of any function demonstrable in the right lobe of the liver 1 month after completion of radiotherapy. This corresponds to the overlap of the field on the liver. The linear sharp cut off between non-function and normal function is well shown (Figs. 1, 2 and 3).

2. The subsequent compensatory increased functional capacity of the remaining unirradiated liver elements which matches the mass now palpable in the epigastrium.

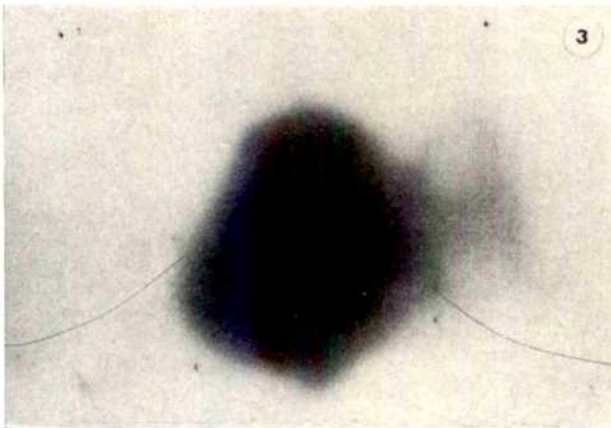


Fig. 3. Scan of liver 18 months after completion of radiotherapy showing recovery of function with hypertrophy of remaining tissue.

Case Report 2

A postmortem examination was carried out on 1 of the 4 patients who died in the immediate postoperative period, 6 weeks after completion of treatment.

The gross liver specimen is shown in the accompanying photograph (Fig. 4) and reveals a sharp line of demarcation between the right side described as "intensely congested almost haemorrhagic with accentuation of the lobular pattern at the edges" and the left side described as "appears swollen and pale yellow in colour".



Fig. 4. Liver specimen showing linear margin between irradiated and non-irradiated zones.

Histologically the picture (Fig. 5) is typical of irradiation liver damage as described by Ingold *et al.* (1965). The general lobular architecture is intact and the portal spaces and peri-portal liver cells are relatively normal.

In the centrilobular region, however, all types of cellular damage are noted with sinusoidal congestion, hyperaemia, severe haemorrhages, loss of cell outline as well as venous dilatation.

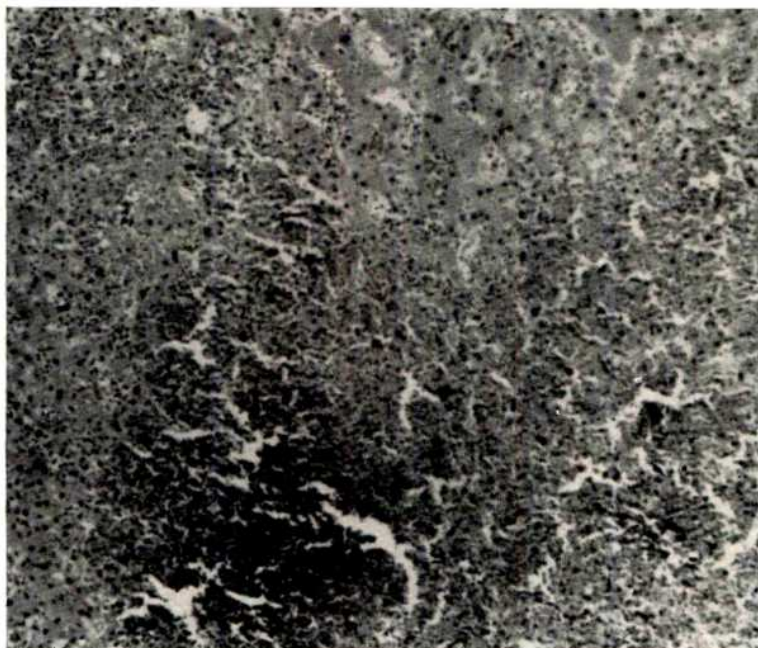


Fig. 5 Histological section of irradiated liver showing cellular damage and haemorrhages.

Side of Tumour

In view of the damage to the liver by irradiation and resultant mortality the survival rates for the 2 sides are compared (Table XVI). It will be seen that the left-sided lesions have a better

Table XVI

Renal Cell Carcinoma Survival—Comparison of Sides

	With Radiotherapy		Surgery only	
	Right	Left	Right	Left
Total	24	25	23	28
Alive	9	11	12	21
Dead—malignant	10	10	11	7
Dead—non-malignant	1	3		
Dead—equivocal	4	0	0	0

prognosis than right-sided and that this difference is mainly apparent in those cases treated by surgery only.

Conclusions

The results reveal that the crude survival time is appreciably higher in the group treated by surgery only and it is during the first 12 months following treatment that the greatest differences are noted. The addition of radiotherapy does not influence the incidence of local recurrence or generalised metastases, but a comparatively large number of cases in the combined treatment group die from coincidental causes of which liver failure as a result of radiotherapy appears significant.

Analysis of results relating to various prognostic factors undertaken in some detail reveals no demonstrable advantage for radiotherapy treated cases including those with venous invasion by tumour, capsular spread, or lymph node metastases or different tumour sizes. There was some evidence of correlation between grade of tumour and prognosis.

At this stage of the trial it appears that postoperative radiotherapy does not have any value in the routine management of hypernephroma. This is judged by crude survival figures. In addition there appears to be a definite danger of radiation liver damage which also precludes the use of radiotherapy in right-sided lesions.

SUMMARY

A randomised trial was started in 1961 in order to assess the value of postoperative radiotherapy in the treatment of hypernephromata.

Crude survival figures covering 2 to 11 years following treatment reveal that those cases treated by surgery only did appreciably better than those treated by combined surgery and irradiation.

Analysis in detail over the first 5 years revealed that the greatest differences in survival between the 2 groups occurred in the first 12 months.

Radiotherapy did not influence the incidence of local recurrence or distant metastases. However, a considerable number of cases receiving radiotherapy died from coincidental causes including radiation liver damage.

Those tumours with histological evidence of venous involvement showed no improvement in survival despite radiotherapy.

Other factors associated with tumour prognosis—size, capsular involvement and node metastases demonstrated no advantage in terms of survival for cases having radiotherapy. Histological grading revealed that grade I tumours have a better prognosis than grade II.

Definite evidence of liver damage was obtained in right-sided lesions irradiated as shown from biochemical liver function tests and isotope scans.

Right-sided lesions did less well than left-sided lesions.

The conclusion reached at this stage of the trial is that postoperative radiotherapy does not appear to have any value in the routine management of hypernephroma.

I would like to thank Professor J. Swinney and Mr W. K. Yeates for their continued co-operation both in the setting up of this Trial and its continuation. I would also like to thank members of the North of England Surgical Society who contributed cases for inclusion in the Trial and Mr C. J. L. Thurgar for his continued advice.

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Renal Carcinoma in Pregnancy

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Renal carcinoma has rarely been reported in pregnant women. This is not surprising since renal malignancy is most common in the 50 to 70 year age group (Fetter and Koppel, 1963; Riches, 1964; Ochsner, 1965), and the ratio of males to females is approximately 2 : 1.

Fetter and Koppel (1963) reported 2 cases of renal carcinoma in pregnant women, and in a review of the literature could find only 13 previously reported cases. These included 2 cases of Wilms' tumour (Esersky *et al.*, 1947; Livermore, 1953). Three additional cases of renal adenocarcinoma have been reported by Penn and Edelstein (1962), Chesley (1969) and Ojo *et al.* (1971).

This report describes 3 cases of renal carcinoma seen in pregnant women between 1966 and 1968. Two of these patients have survived 5 years, the third, 4 years after nephrectomy.

Case Reports

Case 1. This 38-year-old patient was first seen on 13.4.66 at the 16th week of her 3rd pregnancy. She was asymptomatic, but on examination had hypertension (B.P. 150/100 mm Hg) leg oedema and an enlarged right kidney. Hb. 10.8 gm per cent; W.B.C. 5,200 per cu mm with a normal differential count. Blood urea 21 mg per 100 ml. A mid-stream specimen of urine was free of red blood cells, pus cells and organisms. An intravenous pyelogram showed that the calyces of the lower pole of the right kidney appeared to be displaced around a mass. This was suggestive of a cyst rather than a neoplasm, and a further pyelogram after delivery was advised. The patient's leg oedema and hypertension subsided after a few days in hospital, and she was discharged to be supervised at the antenatal clinic.

She remained well until the 33rd week of pregnancy when she was re-admitted to hospital on account of the development of a moderate degree of proteinuria and leg oedema. Microscopic haematuria was present. There were no signs of urinary infection. Gross haematuria and renal colic occurred on the day after admission. Blood pressure was 150/100 mm Hg. The haematuria gradually subsided, and was absent by the 36th week of pregnancy, but the blood urea had then risen to 56 mg per 100 ml. The blood pressure remained unchanged. One week later the blood urea was 60 mg per 100 ml, there was slight pain in the renal angle but no haematuria or bacteriuria, and labour was induced. This was followed by the spontaneous delivery of a normal female infant weighing 3,272 g.

On the 4th day of the puerperium the patient had an attack of acute pyelonephritis which responded to sulphonamides. At her post-natal visit 6 weeks after delivery she was normotensive. The blood urea was normal. A further I.V.P. showed no change from that done during pregnancy.

The patient defaulted and was not seen until 6 months later when she was readmitted with gross haematuria and right-sided renal colic. B.P. 170/90 mm Hg. Blood urea 43 mg per cent. Chest X-ray was normal. *Cystoscopy* showed blood discharging from the right ureteric orifice; a retrograde pyelogram showed no filling of the lower right calyces. A renal arteriogram showed a highly vascular mass in the lower pole of the right kidney.

At operation the lower pole of the right kidney was found to have been replaced by a well encapsulated greyish-brown tumour mass 7.0 × 6.0 × 5 cm. A nephrectomy was performed.

Histological examination showed a well differentiated adeno-carcinoma and marked chronic pyelonephritis in the adjoining renal tissue. There was no involvement of the renal vein and no lymph node metastases were found in the operation specimen.

The postoperative course was uneventful, and the patient has remained well and was apparently free of metastases when last seen 5 years after nephrectomy.

Case 2. This 27-year-old patient was first seen on 7.12.66 at the 11th week of her 3rd pregnancy. She gave a 3-week history of increasing pain in the joints of both lower limbs, frequency of micturition, dysuria and backache. She looked ill and was unable to walk. Temperature 101°F. Her blood pressure was 150/90 mm Hg and she had a heavy proteinuria. The right kidney was grossly enlarged, firm and non-tender. There was marked limitation of movement of both lower limbs due to pain, an effusion in the left knee and gross pitting oedema of both legs.

Hb. 12.0 g per cent, W.B.C. 8,700 per cu mm, E.S.R. 122 mm in the first hour. Blood urea 19 mg per 100 ml. Coagulase positive staphylococcus with a plate count over 100,000 per cu mm was cultured from the urine; L. E. cells were not demonstrated in the peripheral blood. Total proteins 8.6 g per cent, albumin 3.0 g per cent, globulin 5.6 g per cent; electrophoresis showed a slight increase in gamma globulin and a slight decrease in albumin. She was treated with nitrofurantoin 100 mg and aspirin 15 g 6-hourly. The albuminuria disappeared by the 3rd day, and by the end of 1 week she was afebrile and the arthralgia and effusion in the right knee had subsided. Subsequent urine cultures were sterile. I.V.P. showed a space-occupying lesion in the lower pole of the right kidney. A clinical diagnosis of renal carcinoma was made. A renal arteriogram, limited to 5 films, after screening off the uterus, was performed at the 15th week of pregnancy. Around the periphery of this mass and at its junction with the kidney there were several abnormal vessels. The appearances suggested a cystic renal carcinoma.

At operation performed 1 week later, a cystic mass measuring 7.5 cm in diameter, attached to the middle portion of the right kidney, was found. A nephrectomy was performed.

Histological examination showed a clear cell carcinoma, without involvement of the vein or evidence of lymph node metastases.

The patient's subsequent antenatal course was uneventful and she was delivered spontaneously at term of a normal female infant weighing 3,270 g. Postpartum tubal ligation was performed.

The patient was alive and well when last seen 5 years and 4 months after nephrectomy. The baby was healthy.

Case 3. This 42-year-old patient was first seen on 3.2.68 at the 14th week of her second pregnancy. Having previously had a myomectomy, her first delivery in 1964 had been by elective Caesarian section. On examination, a firm irregular mass of limited mobility and approximately 12 cm in diameter was felt in the left upper quadrant of the abdomen. This mass had been present for approximately 1 year and produced no symptoms.

B.P. 120/60 mm Hg, Hb. 11.1 g per cent. Urinalysis normal. Urine cultures were sterile. Blood urea 13 mg per 100 mls.

A provisional diagnosis of an ovarian tumour was made and laparotomy was performed at the 15th week of pregnancy.

A firm, highly vascular retroperitoneal mass attached to the lower pole of the left kidney was found; the right kidney and both ovaries were normal. Left nephrectomy was performed and 3 small regional lymph nodes removed. The tumour was 12 cm in diameter and well encapsulated.

Histological examination showed a clear cell carcinoma with metastatic tumour in the lymph nodes, but no extension into the renal vein.

The patient's subsequent antenatal course was uneventful. Another Caesarian section was performed electively at the 39th week of pregnancy, combined with tubal ligation: a live male infant weighing 3,550 g. was delivered. There was no evidence of local recurrence of tumour in her abdomen.

When last seen 4 years and 3 months after nephrectomy she was well, and X-rays of chest and skeleton showed no evidence of metastases.

Comment

The early diagnosis of renal carcinoma may be difficult because of the variable mode of presentation, or as in Case 3, the lack of symptoms until the tumour has reached a considerable size. The rarity of renal carcinoma in pregnant women, and the reluctance to undertake full radiological investigations during pregnancy, is likely to make the diagnosis even more difficult.

The majority of reported cases of renal carcinoma in pregnant women have presented with a mass in the flank or upper abdomen, associated with one or more of the following: haematuria, loin pain, pre-eclampsia, hypertension and proteinuria. The finding of an enlarged kidney in a pregnant woman, particularly if associated with the features mentioned, therefore warrants further investigation, even in early pregnancy. The authors have seen only 5 cases of renal enlargement in pregnant women in the past 9 years. Three of these are the renal carcinomas reported in this paper; the others were a painful infected cyst and an asymptomatic hydronephrosis due to pelvi-ureteric obstruction.

The Jamaica Cancer Registry lists 49 cases of renal adeno-carcinoma in the decade 1960-69. Nearly half (24) of these were in women, and a fifth of these women were below the age of 30 years. This comparatively high incidence in young women correlates with our having seen 3 pregnant women with renal carcinoma.

Two of the previously reported patients with renal carcinoma in pregnancy have survived 10 years, and 1 for 20 years after nephrectomy (Fetter and Snyder, 1963). The 3 reported here being

alive and apparently free of metastases at 5, 5 and 4 years respectively after nephrectomy are among the longest survivors of our cases of malignant renal tumours—of the other 28 renal tumours treated by nephrectomy in our hospital since 1954, only 1 has survived 5 years and 3 are alive at 3 years.

The number of cases is, of course, far too small from which to draw any valid statistical conclusions but it is tempting to speculate that tumour spread was in some way controlled by the hormonal state during pregnancy.

Summary

Three cases of renal adeno-carcinoma in pregnant women are reported. Two have survived 5 years and the third, 4 years. These survival times are longer than those of adeno-carcinomas in non-pregnant women and in males at this hospital.

We wish to express our thanks to The Jamaica Cancer Registry, to Dr Eric Bateson, who performed the radiological investigations in the first 2 cases, and to Mr N. S. Padmanabhan, who performed the nephrectomy on Case 3.

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The Detection and Prediction of Acute Rejection Episodes in Human Renal Transplants using Radioactive Fibrinogen¹

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There is good evidence that fibrin is deposited in vessels, glomeruli and the interstitium of human renal transplants undergoing rejection. Such deposits have been found in sections of rejected renal transplants by light and electron microscopy (Porter, 1967) and by immuno-fluorescence (McKenzie and Whittingham, 1968). Hobbs and Davies (1960) observed in rats that injected radioactive labelled fibrinogen is incorporated in forming fibrin deposits. Salaman (1970, 1972) and Yeboah, Shackman and Chisholm (1972) have reported the detection of fibrin deposits in rejecting human transplant kidneys by the use of external scintillation counting.

Patients and Methods

51 studies were carried out in 45 patients after renal transplantation. The detector system used for external counting consisted of brass collimated sodium iodide crystal (2.5 cm × 2.5 cm) coupled to a single channel scale/ratemeter (Nuclear Enterprises SR3). The thyroid gland was blocked with 60 mg of potassium iodide or sodium iodide given orally 24 hours prior to the administration of fibrinogen and then daily for 10 days, or on some occasions an intravenous injection of 85 mg sodium iodide was given. 100 microcuries of ¹²⁵I labelled human fibrinogen (obtained from Radiochemical Centre, Amersham, Bucks.) was then given intravenously. One hour after injection of the fibrinogen, the patient emptied the bladder and the count-rates over the heart, transplanted kidney, contralateral iliac fossa and the bladder were measured. The counting time was sufficient to ensure that an initial heart count of at least 10⁴ was obtained. Several days after injection, longer counting times were necessary to maintain adequate counting statistics. The reproducibility of a count was within $\pm 4\%$. Venous blood samples were taken at 15, 30 minutes and on subsequent days to obtain the labelled fibrinogen blood levels.

The data obtained were analysed by 2 methods. The count-rate for each site was expressed as a percentage of the count-rate measured 1-2 hours after injection (Day 0). These values were then plotted daily to obtain the clearance slopes. In addition, the daily count-rate for the transplant site was expressed as a percentage of that obtained for the heart.

Routine immunosuppression consisted of 1,800 mg hydrocortisone (equivalent to 300 mg prednisone) given daily for 3 days and then reduced by half every 3 days until a maintenance dose of 15 mg/day was achieved. Azathioprine was given orally (2 mg/kg body weight/day) but the dose was reduced if thrombocytopenia and/or leucopenia occurred. For anti-rejection therapy, increased doses of prednisone (300 mg/24 hours) were used for 3 days and then reduced by half every 3 days until a maintenance dose was reached. On occasions, this anti-rejection therapy was combined with heparin (40,000 units/24 hours) by continuous infusion. Ancrod (Arvin) has also been used and, in another instance, 1 g prednisone was given intravenously and the dose repeated after 48-72 hours (Bell *et al.*, 1971).

¹ Based on Surgical Research Society communication in January 1972.

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The following criteria were used to detect rejection: increased endogenous serum creatinine, blood urea and 24-hour urinary protein, a reduction in creatinine clearance (g.f.r.), 24-hour urine volume and urea excretion, a reduction in the platelet count, an unexplained pyrexia and the presence of pyronin-positive cells in the urine. Diagnosis was rarely based on a single criterion and a change in 2 or 3 measurements was required. Biopsy of the transplanted kidney was not done as a routine but was limited to those cases with prolonged oliguria; biopsies were also obtained if the patient required exploration to exclude ureteric obstruction, vascular complications or if there was acute tubular necrosis (Kauffman *et al.*, 1964; Chisholm *et al.*, 1969).

Table**¹²⁵I Fibrinogen Studies in 45 Patients**

	No. of Studies	Results	
		Positive	False Positive
Controls	12	0	2
Rejection episodes under* 50 post-transplant days	18 + 6†	24	0
Rejection episodes over 50 post-transplant days	12	0	2
Oliguric patients††	3	0	2
Totals	51	24	6

* $P < 0.001$.

† Oliguric and acute rejection.

†† Oliguric patients—2 acute tubular necrosis + haematoma (false positive);
1 renal infarct (negative result).**Results**

The results for the 51 studies (Table) were examined in the following groups:

Control Patients (Fig. 2)

12 studies were performed on 10 patients with no clinical or biochemical evidence of rejection. There was no significant difference between the ¹²⁵I fibrinogen clearance slopes for the heart and transplant sites ($P < 0.05$). The average value for the maximum transplant/heart ratios for these patients was $88.6 \pm 3.5\%$ occurring after 2.2 ± 1.5 days (Fig. 1). In 2 studies in this group with urine extravasation, the highest ratio was 177% which occurred prior to exploration. In 2 other patients with pathological diagnosis of perinephric abscess, the transplant/heart ratio did not exceed 90% during the period of study.

Acute Rejection Episodes in Transplants within 50 days (Fig. 3)

24 studies were performed on 21 patients in this group. The diagnoses in 12 patients were based on clinical, biochemical and histological evidence (from either biopsy or transplant nephrectomy). In the remaining 12 studies on 9 patients, diagnoses were based on clinical and biochemical evidence only. In this group, average values for the ¹²⁵I fibrinogen clearance slopes for the heart and transplant sites were significantly different ($P < 0.001$). The average value for the maximum

transplant/heart ratios was $206 \pm 70\%$ which was significantly different from the control group ($P < 0.01$) (Fig. 1).

Prediction of Rejection in Grafts within 50 days

In 12 patients the increased deposition of fibrin in the transplant preceded the biochemical and clinical evidence of rejection by 2 to 20 days. One such case is shown in Figure 4.

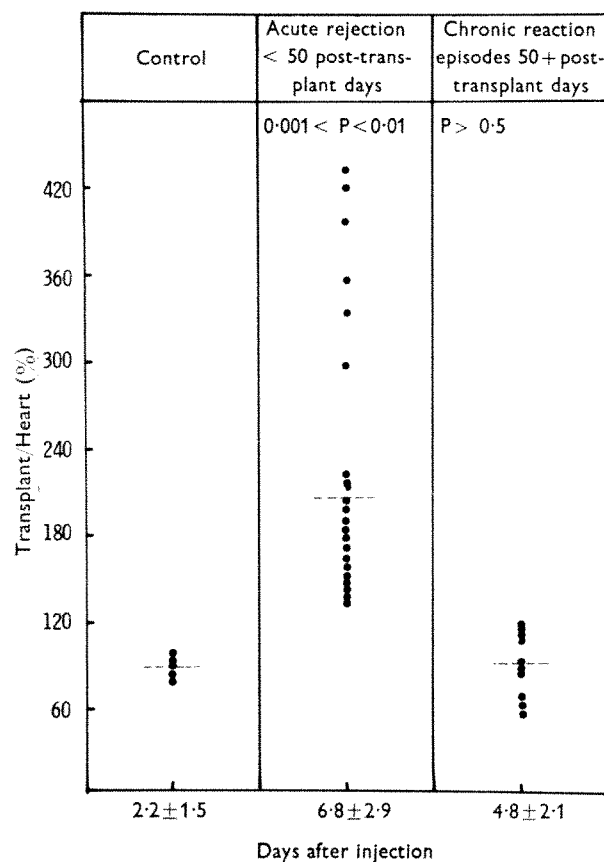


Fig. 1. Maximum transplant/heart count-rate ratios for control group and rejection episodes.

Oliguric Patients

Nine patients were studied within the first 23 post-transplant days; 6 of these had histological evidence of acute rejection and all showed increased transplant radioactivity. In 2 patients with acute tubular necrosis, increased transplant/heart count-rate ratios were due to fresh haematoma following exploration in one and haemodialysis in another (Fig. 5). In 1 patient with renal artery thrombosis, the ratio did not exceed 100% in 10 days of study.

Rejection Episodes in Grafts after 50 days (acute-on-chronic rejection) (Fig. 6)

12 studies were performed on 11 patients. In 10 studies there was no evidence of increased fibrin deposition in the transplant and the average value of the maximum transplant/heart count-rate

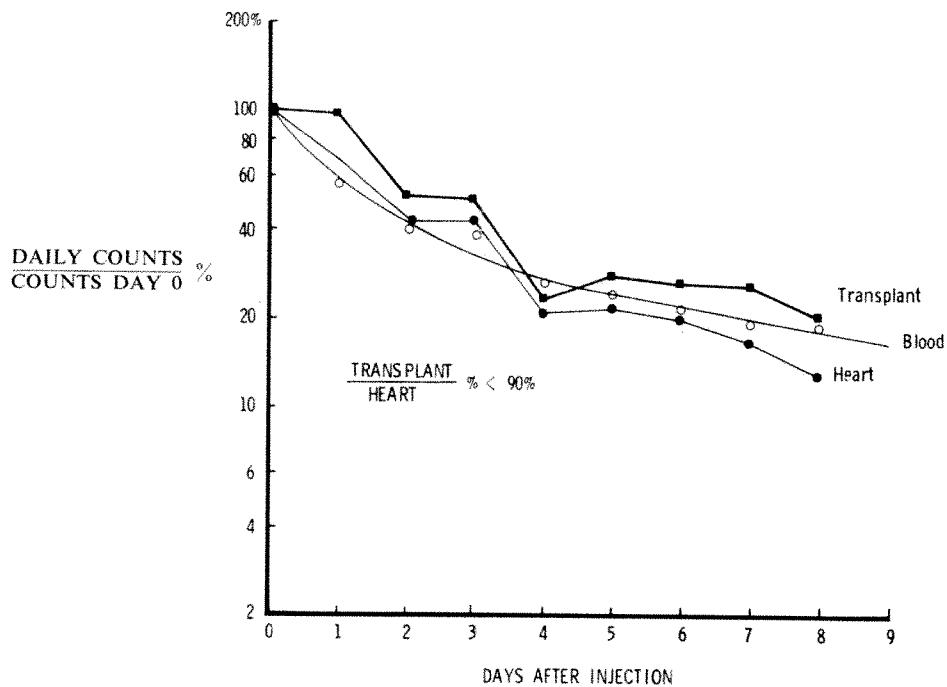


Fig. 2. Control patient (male aged 31). In this patient, with a good functioning transplant, the transplant/heart ratio did not exceed 90%. The clearance slopes for ^{125}I fibrinogen for the blood, heart and transplant were similar.

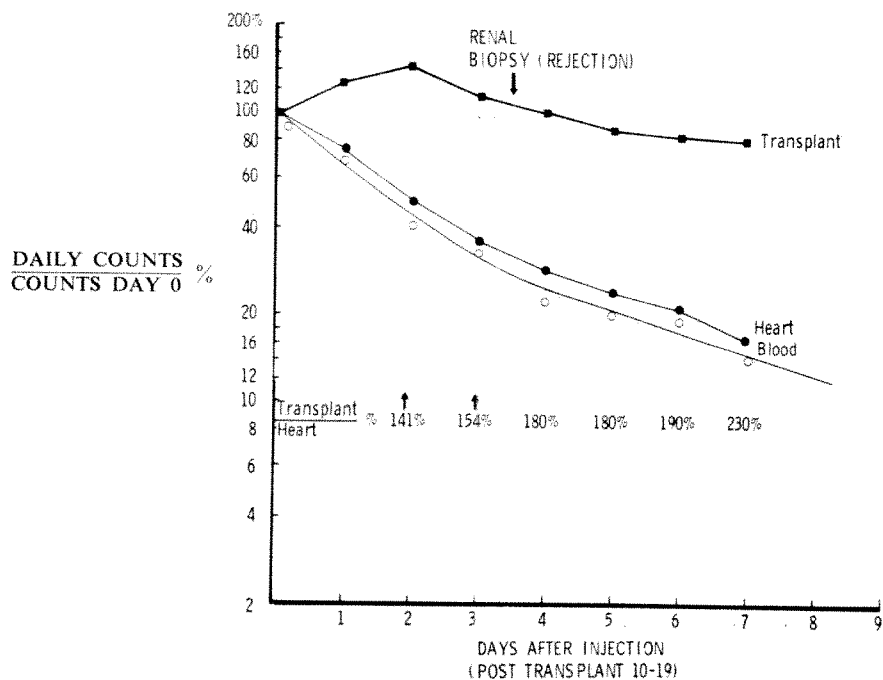


Fig. 3. Acute rejection (male aged 42). Acute rejection occurring during oliguric period was first diagnosed by increased transplant radioactivity and confirmed by renal biopsy. The radioactive fibrinogen clearance slopes for the heart and blood were similar whilst that for the transplant showed fibrin deposition. Anti-rejection therapy using prednisone and heparin did not achieve restitution of renal function.

ratios was $91.5 \pm 22.1\%$ which was not significantly different from the average value in the control group (Fig. 1). For the remaining 2 patients, one with malakoplakia and the other undergoing anicrod therapy, there were ratio increases to 147% and 152% respectively, occurring on the 7th day after injection.

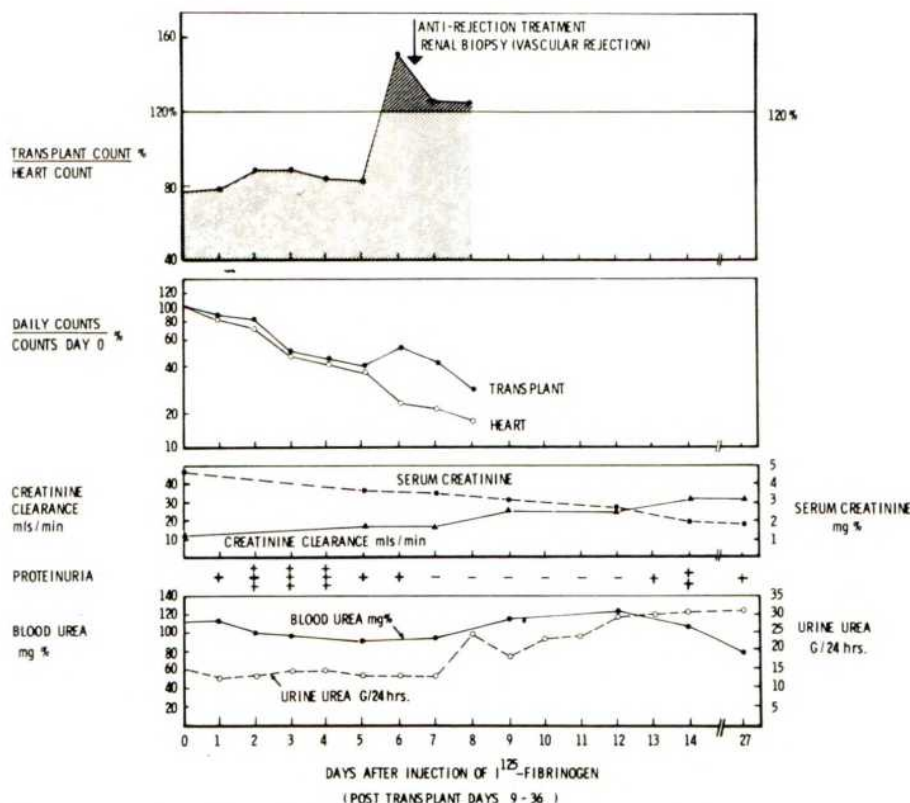


Fig. 4. Acute rejection: Correlation between isotopes and biochemical measurements. Increased transplant radioactivity occurred at a time when biochemical changes were equivocal with urine output between 2 and 3 litres/24 hours. A sudden rise in transplant clearance slope occurred at the time of a fall in the heart clearance slope. Proteinuria could have been due to the renal amyloidosis in this patient. Anti-rejection treatment, by increased doses of prednisone resulted in improved renal function.

False Positive Results

There were 6 patients (12% of total studies) with false positive results. Two were due to extravasation of urine, 2 oliguric patients had proven haematomata, 1 patient had malakoplakia and another gave a false positive result during anicrod therapy (Fig. 5). The averages for the ^{125}I fibrinogen clearance slopes in these patients showed significant differences between the heart and transplant sites ($P < 0.01$).

Discussion

Our studies have shown that this technique is a useful aid in the detection of acute rejection episodes in the first 50 days after transplantation, (Salaman, 1970, 1972; Yeboah *et al.*, 1972).

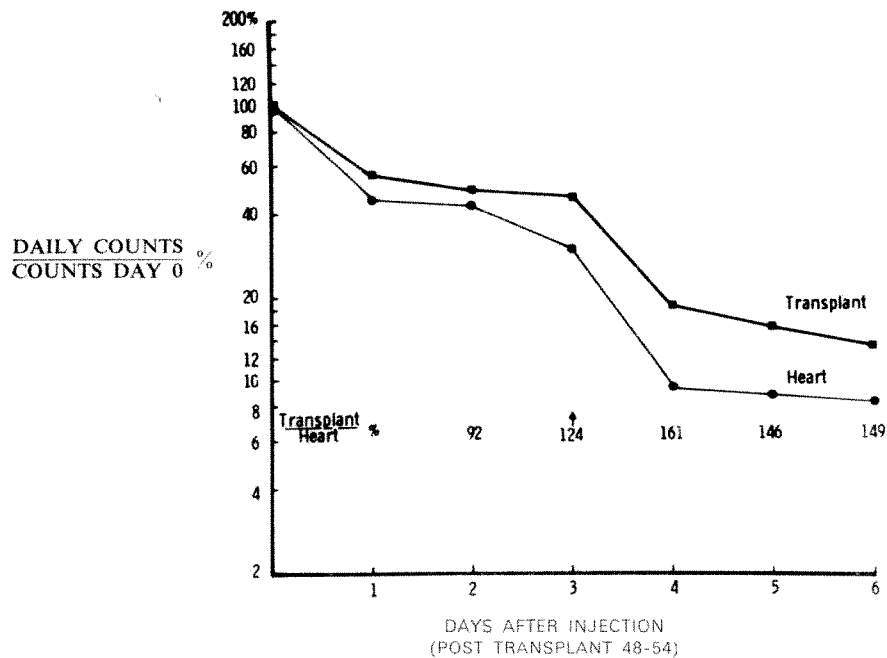


Fig. 5. Necrotic kidney and haematoma (male aged 47). False positive results occurred with the formation of a haematoma during dialysis in this oliguric patient with a necrotic transplant kidney. The radioactive fibrinogen clearance slopes for transplant and heart were not significantly different.

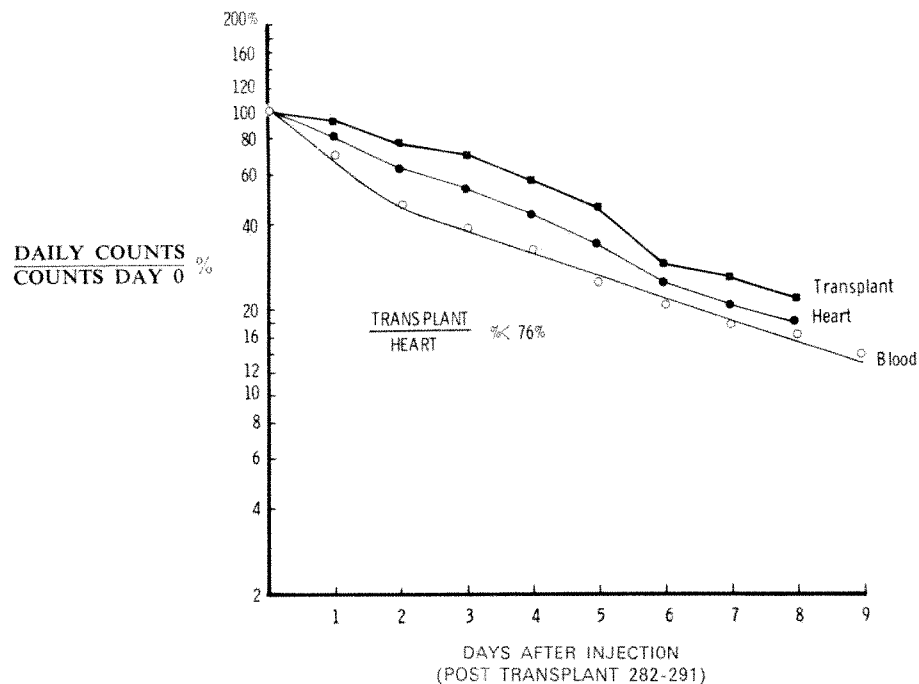


Fig. 6. Rejection episode in chronic rejection (male aged 39). Acute-on-chronic rejection episode with no increase in transplant/heart ratio but subsequent transplant histology confirmed the diagnosis of chronic rejection. The radioactive fibrinogen clearance slopes for transplant, heart and blood are similar.

The procedure is especially useful in oliguric patients to distinguish between acute rejection and other causes of oliguria such as acute tubular necrosis and renal artery thrombosis.

In patients undergoing haemodialysis, the risk of developing a haematoma is increased and the interpretation of ^{125}I fibrinogen results without supportive clinical evidence may lead to a false diagnosis of rejection. The possibility of radioactive fibrin being incorporated into a forming haematoma is minimal if the fibrinogen is administered when the drains have been removed from the operative site. In the work presented here, the normal practice has been to administer the dose of fibrinogen between the 5th and 10th post-transplant day. The procedure has been found to be reliable in predicting rejection episodes in the first 50 days after transplantation although, when the diagnosis is not supported by biochemical evidence, renal biopsy may be advisable. We have not obtained any positive results with rejection episodes that occurred after the 50th post-transplant day (Yeboah *et al.*, 1972), in contrast with the observations made by Salaman (1970, 1972).

In the interpretation of results, examination of the fibrinogen clearance slopes for the transplant and heart sites was found to provide the best indication of acute rejection episodes. In addition, the possibility of eliminating false positive results is enhanced by reference to the clearance slopes for individual patients. The use of a transplant/heart count-rate ratio has also been shown to provide an indication of acute rejection episodes. The adoption of an arbitrary value of 120% for this ratio appears to provide a means of predicting acute rejection episodes (Fig. 1), but the use of such an index is more liable to lead to false positive results especially several days after the administration of the fibrinogen when count-rates are much lower.

The prediction of possible rejection episodes by use of the fibrinogen test should be interpreted as a warning to investigate even small changes in the standard clinical measurements used for the detection of rejection. It is possible that with further experience with this technique, the clinician may be prepared to begin anti-rejection therapy on this evidence alone.

Summary

The results of the use of ^{125}I fibrinogen in 51 studies performed on 45 patients after renal transplantation are reported.

The control patients did not show increased transplant radioactivity and there was no significant difference between the clearance slopes of the heart and transplant sites.

All 24 studies of acute rejection episodes within the first 50 days after transplantation showed increased transplant radioactivity with a significant difference between ^{125}I fibrinogen clearance slopes of the heart and transplant sites.

Rejection episodes were predicted in 12 patients before clinical and biochemical evidence of rejection.

There were no positive results with rejection episodes occurring more than 50 days after transplantation.

False positive results were obtained with haematomata, urinary leak, malakoplakia and during anocord therapy, although in some cases these can be recognised by examination of the clearance slopes.

The technique is a useful aid in the diagnosis of acute rejection episodes in transplants within 50 days of the operation but not in chronic rejection.

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Aneurysms in Human Renal Homografts

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The histology of human renal homotransplants was first described by Hume *et al.* (1955) and there have been many subsequent accounts. Some of the descriptions refer to the rupture or disappearance of the arterial elastica as a result of fibrinoid necrosis (Porter *et al.*, 1963; Porter *et al.*, 1964; Porter, Marchioro and Starzl, 1965). Only Dempster, Harrison and Shackman (1964) mention aneurysmal dilatation of arterioles seen histologically, but Darmady, Offer and Stranach (1964) describe them in transplanted kidneys retrieved at postmortem and subjected to microdissection, a technique which permits whole vessels to be seen in isolation.

Examination of whole organ sections, 300 μ thick, of 3 transplant-nephrectomy specimens after arterial injection suggests that aneurysms may be very widespread in the cortex and that a simple "three-dimensional" method such as this may give information not yielded by study of thin paraffin sections.

Specimens

The 3 transplanted kidneys were removed because of functional failure 49, 56 and 58 days after transplantation. In each case arterial and venous blood-flow appeared satisfactory at transplant-nephrectomy.

Methods

After removal each kidney was kept at room temperature while it was taken to the laboratory and cannulated. Normal saline was passed through the arterial cannula until clear saline emerged from the venous cannula. Blue radio-opaque Colorpaque (Pilot Chemicals Ltd) in 70% solution and containing gelatine (5 g/100 ml) was injected through the arterial cannula at 37°C at a pressure not exceeding the systolic blood pressure of the patient. The kidney was then X-rayed.

After a week's fixation in buffered 10% formol-saline, the kidney was bisected in the coronal plane. One-half was used to make whole-organ serial sections (Whimster, 1970) and slices for clearing by the Spalteholz method (Culling, 1963) and blocks for histology were taken from the other half. Whereas the paper sections were ready within 24 hours, the clearing technique took 6 months.

The paper sections and the cleared slices were examined with a dissecting microscope (up to $\times 70$) by transmitted light, and then further examined with a binocular microscope with micro-photographic attachment.

For control purposes, several apparently normal kidneys removed at postmortem were processed and examined in the same way.

Results

The normal control kidneys showed good filling on X-ray (Fig. 1). In paper sections and cleared slices this was confirmed (Fig. 2), the majority of interlobular arteries, afferent arterioles, and glomeruli being seen to contain the Colorpaque. Although the vessels showed the normal helical configuration, no aneurysms were seen.

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The arterial injection produced patchy filling of the vessels in the transplant-nephrectomy kidneys as seen on X-ray (Fig. 3), and the vessels appeared narrower and more spider-like than those in the control kidneys. The paper sections and cleared slices confirmed these findings and also showed numerous haemorrhages (Fig. 4) and some infarcts. Under the microscope, the aneurysmal dilatations, once observed, were easily found (Figs. 5, 6 and 7) in all 3 cases. They were present on afferent arterioles and interlobular arteries but not on the arcuate and larger arteries, nor on medullary arteries.

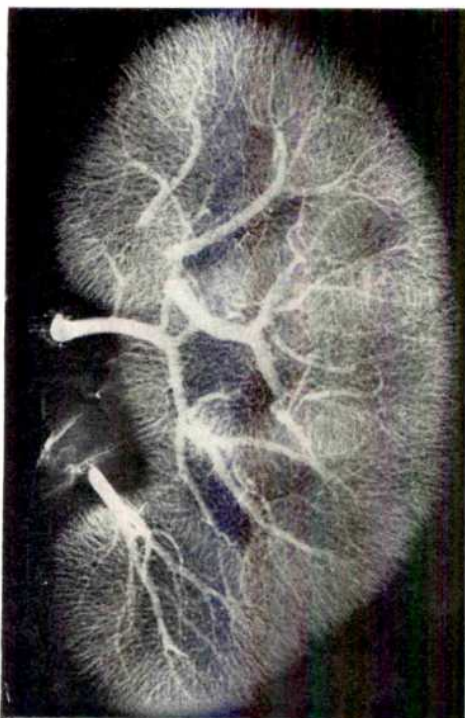


Fig. 1. X-ray of injected normal postmortem kidney.



Fig. 2. Paper section of injected normal postmortem kidney: cortex. (original magnification, $\times 50$)

Areas of haemorrhage were searched for ruptured aneurysms but none could be identified with certainty, although aneurysms were present in these areas.

Examination of paraffin sections revealed the vascular changes described previously (Porter *et al.*, 1963; Porter *et al.*, 1964; Dempster *et al.*, 1964; Porter *et al.*, 1965), that is, fibrous intimal proliferation, loss of elastic tissue and medial scarring. Neither fresh fibrinoid necrosis nor recent thrombosis was seen. Aneurysmal dilatation of vessels was found only after careful search—a situation very different from the ease with which aneurysms were found on examining the paper sections and cleared slices. The probable reason for this apparent paradox is that scrutiny of 300 μ thick paper sections of bisected kidneys and of cleared slices permits rapid survey of much of the injected arterial system, whereas 5 μ thick sections from paraffin blocks of ordinary size allow examination of a relatively minute amount of it.

Discussion

The aneurysms described here have been seen before in microdissection preparations (Darmady *et al.*, 1964). But microdissection, though it permits the vessels to be seen in 3 dimensions,

necessarily disrupts the renal anatomy and is confined to small areas of kidney. Neither this technique, nor histology with 5- μ sections, give an indication of how widespread the aneurysms may be. The whole-organ sections suggested, and the cleared sections later confirmed, that they may be numerous.

Significant amounts of renal tissue may therefore be damaged by multiple small haemorrhages from such aneurysms. Only patent aneurysms could be injected and rendered visible by the methods employed in this study but others might well have been occluded by thrombus; if this were the case, it would provide a reason for the presence of the numerous small infarcts seen in all 3 kidneys.

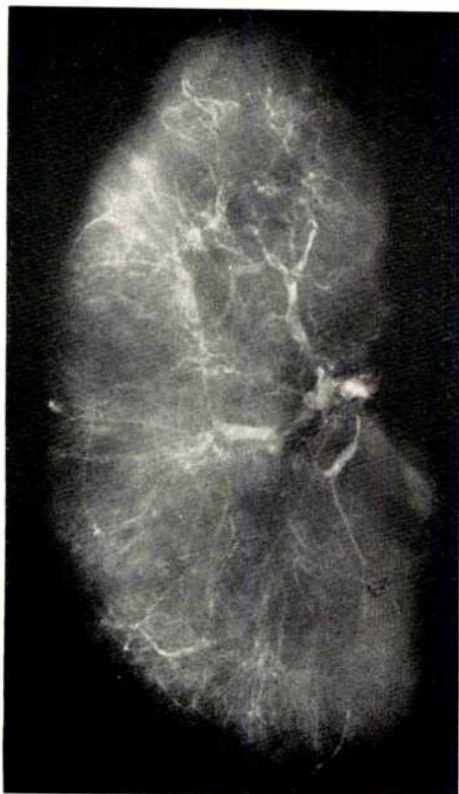


Fig. 3. X-ray of injected transplant-nephrectomy specimen.

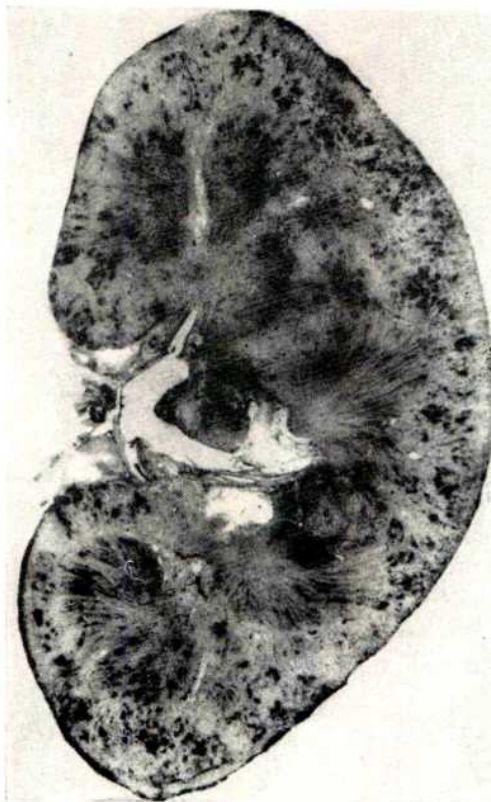


Fig. 4. Paper section of injected transplant-nephrectomy specimen. (Actual size.)

It seems likely that aneurysms are the eventual result of focal destruction by fibrinoid necrosis of the internal elastica and media of arteries during episodes of rejection. These structures are replaced during subsequent healing by fibrous tissue (Fig. 8). Such vascular scars were seen quite frequently in histological sections of our material and may well be the sites of origin of the aneurysms.

Focal necrosis and scarring of vessels are known to occur during graft rejection (Porter *et al.*, 1965) and have been seen as early as 25 days after transplantation (Dempster *et al.*, 1964). Darmady *et al.* (1964) suggest that smaller vessels are affected first, but focal medial necrosis was described in arcuate and interlobar arteries in a patient who died only 25 days after transplantation (Dempster *et al.*, 1964). It might have been expected that in our 3 cases the transplants

had survived long enough for the larger arteries to be affected, but though intimal and medial fibrosis were seen in larger arteries, no aneurysms were found in them.

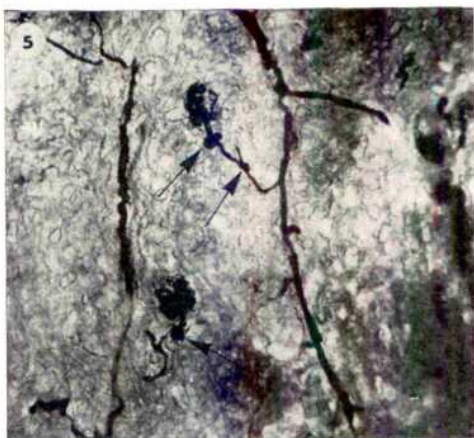


Fig. 5. Paper section of injected transplant-nephrectomy specimen: cortex with aneurysms (arrows). (original magnification, $\times 50$)

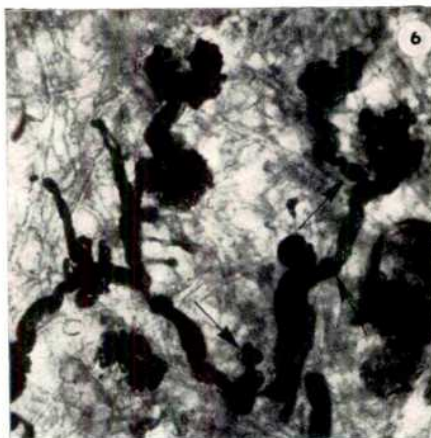


Fig. 6. Paper section of injected transplant-nephrectomy specimen: cortex with aneurysms (arrows). (original magnification, $\times 100$)

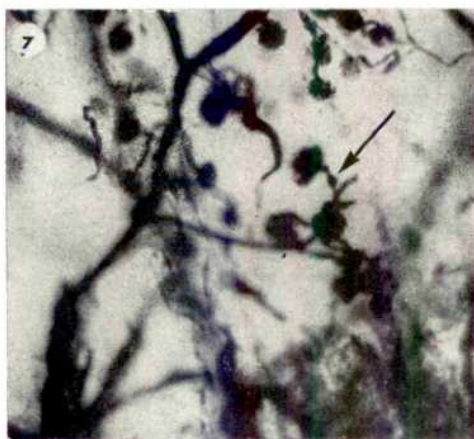


Fig. 7. Slice of injected transplant-nephrectomy specimen cleared by Spalteholz method: cortex with aneurysm (arrow) and irregular vessels. (original magnification, $\times 50$)

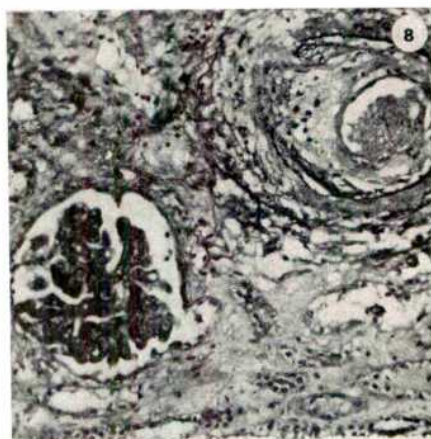


Fig. 8. Interlobular artery containing injection mass (also in adjacent glomerulus) and showing ruptured internal elastic lamina, medial damage and intimal fibrosis. (original magnification, approx. $\times 160$)

Summary

Numerous aneurysms have been found on interlobular arteries and afferent arterioles in 3 kidneys obtained at transplant-nephrectomy after 49, 56 and 58 days, using whole-organ sections $300\ \mu$ thick, after arterial injection with a radio-opaque medium. These sections, and also slices cleared by the Spalteholz technique, give a 3-dimensional picture when viewed with transmitted light.

It is suggested that the function of renal transplants may be impaired by haemorrhages from these small aneurysms and by small infarcts when thrombosis occurs in them.

We desire to thank Dr John Moorhead, Physician in Charge of the Renal Unit, Royal Free Hospital, from whose patients these kidneys were obtained. We wish also to thank Mr Graham Glazzard, FIMLT, and Mr George De Freitas for much technical assistance.

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Evaluation of Hydronephrotic Damage using Nitroblue Tetrazolium

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The urologist is not infrequently confronted with the problem of the extent of injury in a kidney which has been obstructed for an unknown length of time. Such tests as excretion pyelography, renography, renal scan, or creatinine clearance may give a good indication of the degree of damage but often the surgeon is left with having to make a decision based on the gross appearance of the kidney at operation. Laboratory studies by Schirmer and co-workers (1966), using manometric techniques, found that if renal obstruction was allowed to progress for 42 days there was a shift in metabolism from aerobic to anaerobic. Evaluation of cell respiration may also be performed with the use of various so-called electron acceptors (Wainio, 1970). These include dichlorophenolindophenol, ferricyanide, methylene blue, phenazine methosulfate, and tetrazolium chlorides. These agents undergo change, by reduction, in the absorption of light as measured on a spectrophotometer. Kun and Abood (1949) have demonstrated that the kidney is one of the most metabolically active organs as evidenced by succinate-tetrazolium activity. Subsequently, Slater, Sawyer and Strauli (1963) have demonstrated points in the electron transport system of the cell mitochondria where succinate-tetrazolium coupling occurs. Terasaki, Martin and Smith (1967) utilised a simple test in which the colour change of tetrazolium by renal tissue as seen with the unaided eye was used to estimate the degree of ischaemic damage. Although simple to perform, the estimation of colour change requires considerable practice and is subject to inconsistencies. Therefore, to measure the degree of hydronephrotic damage a precise and reasonably rapid method was devised based on a modification of more complicated assay techniques (Slater *et al.*, 1963; Wainio, 1970). The aim was to try to demonstrate whether there was any difference between the normal kidney and those that have undergone varying degrees of damage from hydronephrosis.

Methods and Materials

The male Wistar rat was selected as the experimental animal. In this study the ureter of one kidney was ligated at the ureteropelvic junction. Control studies were done and then at intervals of 1, 2, 4 and 6 weeks the kidneys were removed and sectioned for microscopic study as well as assayed using nitroblue tetrazolium. The test is performed under aerobic conditions at room temperature in about 30 minutes and uses a spectrophotometer to measure the change in absorbency at 560 m μ .

The kidney tissue was prepared by homogenising a wedge of renal tissue (2-3 mm wide and weighing about 300-400 mg) including cortex and medulla in 0.25 molar sucrose (5°C) so as to make a 10% W/V tissue preparation. The homogenate was then centrifuged at room temperature at 2,000 r.p.m. for 10 minutes to separate out cellular debris. The tetrazolium solution was prepared by adding nitroblue tetrazolium to a potassium-phosphate buffer, pH of 7.4, 25°C so

as to make a concentration of 0.1 mg/ml of the tetrazolium salt. A blank solution of 4.8 ml distilled water and 0.2 ml of the supernatant from the homogenate was prepared and the spectrophotometer set at 0 absorbency at 560 m μ . Then 0.2 ml of the supernatant from the homogenate was added to 4.8 ml of the tetrazolium-KPO₄ solution. A change in absorbency was registered on a spectrophotometer at 560 m μ . In this study the change in absorbency or transmission at the end of 15 minutes was used.

Results

Nitroblue tetrazolium produced a definite and consistent value for the control kidneys and tissue from the chronically obstructed kidneys at 6 weeks produced values significantly different from the controls (Fig. 1). However, the values at 1, 2 and 4 weeks did not differ significantly. At the

Absorbance-log T Transmission.

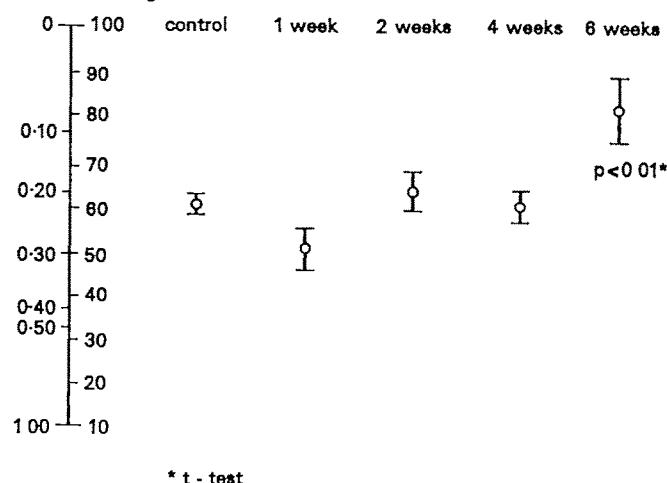


Fig. 1. Light absorption of nitroblue tetrazolium in hydronephrosis. Each value represents mean and standard deviation in 5 experiments.

end of 1, 2 and 4 weeks, examination of microscopic sections revealed progressive dilatation of the tubules and at the end of 6 weeks, hydronephrotic atrophy was marked.

Interpretation

The energy for various cellular functions in the mammalian kidney, particularly the reabsorptive processes, is derived from oxidative metabolism. The reduction of tetrazolium by renal tissue is but a part of the complex process accompanying cellular oxidation. This study indicates when a rat kidney is markedly damaged as judged by the ability to reduce nitroblue tetrazolium. This seems to correlate with gross and microscopic evidence of severe parenchymal destruction. Other investigators have found renal enzyme activity to vary with hydronephrosis. Kissane and Heptinstall (1964) reported that alkaline phosphatase activity in the proximal tubule of the rat decreased as early as the second day after obstruction; they also found that the activity of glucose 6-phosphate dehydrogenase was increased. Eranko and Niemi (1954) demonstrated a histochemical decrease in phosphatase activity in rat and rabbit kidneys after 16 days' obstruction although some nephrons still demonstrated normal phosphatase activity. In the study reported here, the severe insult of 6 weeks' duration of obstruction was needed to produce a change in

tetrazolium reductase activity. Yet to be determined is the correlation between recovery of function and tetrazolium reducing activity.

This test may have a clinical application where the surgeon wishes to measure the degree of damage in an obstructed kidney either for prognosis or to exclude severely damaged kidneys from the reconstructive procedures.

Summary

A test for kidney viability, using nitroblue tetrazolium, has been evaluated in experimental hydronephrosis. A significant difference between control and kidney tissue obstructed for 6 weeks was observed.

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Electromyography of the Detrusor Muscle

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The achievement of urinary continence is possible when the intravesical pressure remains less than that in the urethra (Enhörning, 1961). Much attention has been paid to the cause and detection of bladder neck and urethral sphincter dysfunction and to its treatment (Bates, 1971; Edwards, Harrison and Williams, 1971; Moolgaoker *et al.*, 1972; Vincent, 1972). This paper is particularly concerned with the role of electromyography (E.M.G.) as a means of diagnosing detrusor dysfunction in cases of female urinary incontinence.

In practice, 3 types of detrusor dysfunction can be distinguished:

1. Uninhibited detrusor activity—an unstable bladder.
2. Hypertonic detrusor action.
3. Hypotonic detrusor action.

Although the function of the detrusor was the primary object of interest in this study, its function and activity could not be investigated without a knowledge of the simultaneous activity of the bladder neck and proximal urethra.

Abnormal increased detrusor activity is due either to intrinsic abnormality or is secondary to upper motor neurone disorder or to urinary tract infection. Usually, hypertonic detrusor activity is secondary to upper, and hypotonic activity to lower motor neurone disorder.

In a review of 75 female patients having persistent symptoms of urinary incontinence following a repair operation, Bates (1971) found that 45% had an unstable bladder as detected by means of pressure-flow cystography. Moolgaoker *et al.* (1972) reviewed 95 women who had complained of urinary incontinence and found that 22 were suffering from detrusor instability alone, whilst 17 had both detrusor instability and sphincter dysfunction or urethral narrowing. Both series of patients had been carefully screened to exclude associated neurological disorders.

Hence it would appear that a significant proportion of incontinent women could be expected to suffer from some sort of detrusor instability. The instability has been shown to be demonstrable on pressure-flow cystography. However, no additional evidence has been presented as to the exact aetiology of the primary disturbance. For this reason it was decided to investigate smooth muscle E.M.G. as a possible means for evaluating the nature of this detrusor dysfunction.

Materials and Methods

The patients concerned in this study were attending the Incontinence Unit of the Institute of Urology. All had been subjected to a careful clinical examination and in addition had undergone cystometrogram and urethral pressure profile studies (Harrison and Constable, 1970; Edwards *et al.*, 1971). For the purposes of the present investigation, the following simultaneous measurements were made (Fig. 1):

1. Pulse rate from a photoelectric pick-up on the thumb.
2. Urethral sphincter electromyogram.
3. Detrusor electromyogram.
4. Bladder pressure from a fine urethral catheter and unbonded strain gauge pressure transducer.
5. Rectal pressure via a fine catheter in the rectum connected to an unbonded strain gauge pressure transducer.

6. Urine flow rate obtained by differentiating the continuous output signal from the load cell used to record urine volume.
7. Urine volume obtained by the use of a load cell to monitor the weight of the beaker into which urine was passed.
8. Respiratory rate from a thermistor probe placed beneath one nostril.

An optional recording of the external anal sphincter electromyogram was also available.

Preliminary studies in several female patients under anaesthesia confirmed that it was possible to insert fine wire electrodes via the anterior vaginal wall into the muscle of the trigone or bladder base. This manoeuvre was performed by passing a cystoscope, partially filling the bladder, and transilluminating the anterior vaginal wall through the bladder base (Fig. 2). As the needle

EMG SCHEMA

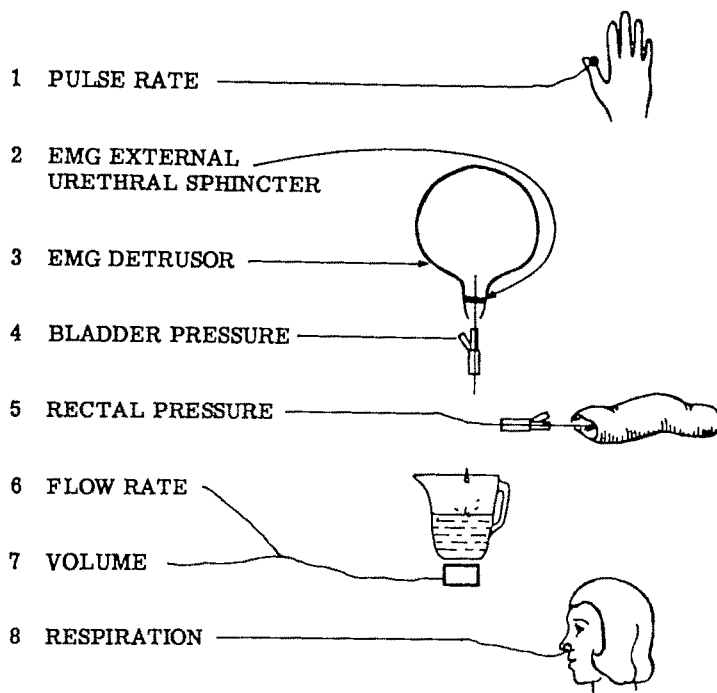


Fig. 1. The various parameters recorded in the investigation of patients with urgency of micturition.

containing the electrode wire was inserted through the anterior vaginal wall into the bladder (Fig. 3), its presence could be detected with the cystoscope. Confirmation was also obtained by small drops of urine appearing at the proximal end of the needle in the vagina. Successful recordings were then made of the detrusor E.M.G. activity.

The technique was next adapted for use with conscious out-patients. Each patient was liberally supplied with cold drinks of her choice as soon as she arrived in the clinic, and encouraged to continue drinking. For introducing the electrodes and recording catheter, the patient was first placed in the exaggerated Sim's position with a nurse holding a Sim's retractor to the left of the operator. The vagina was cleaned with a solution of 0.5% Hibitane in water and 2% Xylocaine was infiltrated into the proposed puncture sites in the vulva, vagina and perineum. Trimel coated silver wire 0.01 in (0.25 mm) in diameter (Johnson & Matthey Ltd.) was passed through an 18-gauge Medicut intravenous cannula. The tip of the wire was bent back along the needle for about 1 mm (Fig. 3).

The patient was asked to "bear down" and some descent of the anterior vaginal wall was noted. The needle and its wire were then inserted into the bladder via the anterior vaginal wall 5 mm to the left of the midline at the area of greatest descent. The initial resistance of the anterior vaginal wall and bladder was felt and then the needle lay free within the bladder cavity as evidenced by drops of urine appearing at its proximal end. A second needle and electrode wire was inserted 5 mm to the right of the midline and its position similarly confirmed. The hooked ends of each wire were then fixed into the bladder wall by withdrawing the needle cannulae and lightly pulling the wires into the detrusor. In our opinion this technique is simpler to use in the out-patient clinic than that described by Boyce (1952).

The external urethral sphincter was localised by introducing a similar wire electrode about 10 mm lateral to the external urethral meatus, 10 to 30 mm deep and parallel to the urethra. The presence of striated muscle E.M.G. activity with a good signal-to-noise ratio was first confirmed using a Medelec type MS4 portable electromyograph. If the results were not satisfactory, the wire was relocated. There should be a marked increase in E.M.G. activity during active contraction of the sphincter. A second wire electrode was introduced on the other side of the meatus.

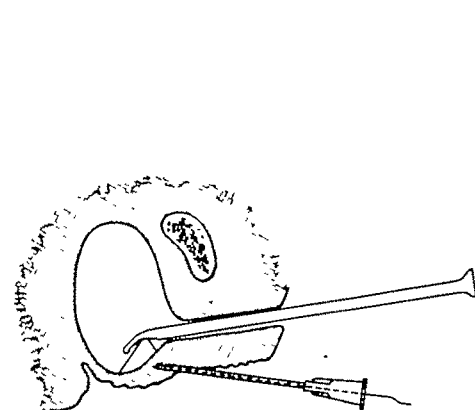


Fig. 2. Transillumination of the anterior vaginal wall through the bladder base.

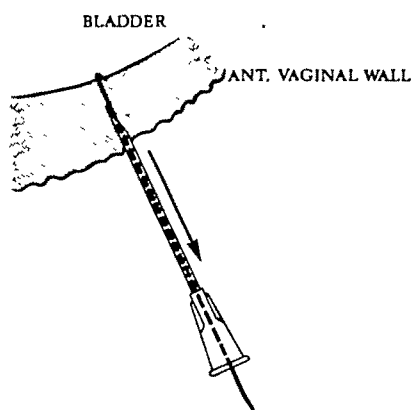


Fig. 3. An E.M.G. electrode remaining within the detrusor muscle as the cannula is withdrawn.

Using the same technique, a pair of wire electrodes was inserted into the external anal sphincter and a satisfactory E.M.G. confirmed using the MS4.

An indifferent electrode for the E.M.G. recordings was obtained by placing an E.C.G. metal plate electrode on the patient's thigh. The patient was then moved carefully on to the modified commode.

The various signals described were recorded on an 8-channel Elema-Schonander Type 81 ink-jet recorder. The detrusor, urethral sphincter and anal sphincter recordings were obtained with type EMT12B universal amplifiers used in conjunction with a type EMT 17 a.c. suppressor input adaptor. With this arrangement EMT recordings could be made at the $10 \mu\text{V}$ level with the patient in an ordinary hospital room without the need for any electrical screening. The striated muscle sphincter E.M.G.s were recorded at gains of 50 or $100 \mu\text{V}$ per centimetre deflection with a low frequency time constant of 0.03 seconds (30% gain reduction at 5 Hz) and an upper cut-off frequency of 700 Hz. The smooth muscle detrusor E.M.G. was recorded with either a gain of 1,000 or $2,000 \mu\text{V}$ per centimetre deflection with a low-frequency time constant of 5 seconds (30% gain reduction at 0.03 Hz) and an upper cut-off frequency of 70 Hz or the amplifier settings used for striated muscle E.M.G.s. The urinary flow rate and volume were recorded using the Uroflow attachment for the Mingograf. This was invaluable in detecting the onset of urine flow.

Bladder and rectal pressures were recorded with Statham P23 pressure transducers feeding type EMT 311 electromanometer amplifiers, the pressure channels being calibrated against a mercury manometer.

Artefacts on the E.M.G. recordings could arise from electrostatic charges generated by staff bending over the patient and by movements of the patient's torso. Particular attention was paid to marking the chart recording when these events occurred. The patient, seated on the commode, passed water into a large funnel leading to a beaker placed on the Uroflowmeter. She was asked to continue to drink as much as possible but to avoid unnecessary movement. She was encouraged to read and was left alone as much as possible. The recorder was located in an adjacent room and the patient observed via closed-circuit television. Recordings were made continuously for periods of 1 to 2 hours at a paper speed of 2.5 mm per second. This was increased to 10 or 100 mm per second whilst the patient was micturating. At the end of the recording session the bladder was catheterised and the residual urine volume noted. A cystometrogram was then performed, a pump being used to fill the bladder at a rate of 50 ml per minute. During the cystometrogram the effect of increasing the fluid volume in the bladder on the various recordings was noted.

The electrodes and catheters were then removed and the patient placed on a prophylactic course of antibiotics. The patients were not upset by these procedures and those who were asked, agreed to have the procedure repeated.

Results

The appearance of a marked degree of activity in the detrusor E.M.G. appeared to be associated both with a state of apprehension and with the desire to micturate. Typically the low-frequency (wave) detrusor E.M.G. had a frequency spectrum of 0.1 to 5 Hz and an amplitude range of approximately 100 to more than 2,000 μ V. There was also a high-frequency (spike) component of the detrusor E.M.G. with a typical spike amplitude of 100 μ V. The effects observed are best illustrated by some case histories.

Case 1. Patient A. M., aged 63. She has persistent incontinence especially during the night and this is aggravated by stress during the day. She has some urgency. No abnormal neurological signs. A cystometrogram revealed a bladder capacity of 450 ml with a residual urine of 50 ml. Frequent detrusor contractions occurred together with leakage. Her urethral pressure profile was normal.

When the patient was relaxed and comfortable with no desire to micturate, the low-frequency detrusor E.M.G. component was substantially less active than just prior to her micturating as evidenced by the wave counts of Table I. Immediately prior to micturition, very large amplitude swings (greater than 1,500 μ V) were seen accompanied by an elevation of the bladder pressure by 35 to 40 mm Hg above the resting pressure. Immediately after micturition, large swings continued in the low-frequency detrusor E.M.G. which then settled down to a relatively low level of activity.

Case 2. Patient A. W. P., aged 60. She has stress incontinence, but is dry at night, and there is no urgency. No abnormal neurological signs. A cystometrogram revealed a bladder capacity of 600 ml. The urethral pressure profile was normal. She was taking 800 mg of flavoxate hydrochloride per day. With the patient relaxed and with no desire to micturate the low-frequency E.M.G. activity was small. It built up prior to micturition as the patient experienced desire to do so, as indicated in Table II. Large amplitude swings were observed during micturition and immediately afterwards. When she was trying to hold back, the urethral sphincter activity was approximately 50 μ V, but during micturition and afterwards it fell to 12 μ V. The large swings in the low-frequency detrusor E.M.G. were not accompanied by swings in the bladder pressure. Subsequent study, 3 weeks after stopping flavoxate hydrochloride, showed an increased activity in the upper frequencies of her low-frequency detrusor E.M.G.

Case 3. Patient V. W., aged 27. She has suffered from disseminated sclerosis for 7 years. Since the birth of her daughter 5 months ago, she has had episodes of urinary retention. Recently she has had urgency. Neurological examination showed increased leg reflexes and extensor plantar responses. The abdominal and anal reflexes were absent. The urethral pressure profile was very high and the bladder capacity 475 ml. Frequent detrusor contractions occurred. There was a good urethral sphincter amplitude of 35 μ V which increased to 70 μ V prior to micturition but which did not diminish during micturition. At the start of the investigation there was marked low-frequency detrusor E.M.G. activity which flattened off as the patient settled down. Characteristically, each time the patient

said her bladder felt full, large amplitude swings in the low-frequency detrusor E.M.G. were evident and it was quite possible to forecast when she was about to micturate (Fig. 4). The swings were about 2.5 mV in amplitude and occurred at 10 to 20 second intervals. The large amplitude low-frequency detrusor E.M.G. swings continued during micturition and ceased soon after. They were not apparently related to changes in bladder pressure, which

Table I

Wave Analysis of the Low-frequency Detrusor E.M.G. of Patient A. M.

Frequency	Number of Waves in a 30-second Epoch	
	Just prior to micturition	Just after micturition
0.1 Hz	2	0
0.2	2	2
0.4	3 (Respiration)	4
0.6	4	2
0.8	7	1
1.0	9 (Pulse)	7
2.0	13	5
3.0	10	7
4.0	4	0
5.0	10	5
	—	—
	64	33
	—	—
	Mean amplitude $\approx 300 \mu V$	Mean amplitude $\approx 100 \mu V$

Table II

Wave Analysis of the Low-frequency Detrusor E.M.G. of Patient A. W. P., on 800 mg flavoxate hydrochloride per day

Frequency	Number of Waves in a 60-second Epoch	
	No desire to micturate	Strong desire to micturate
0.1 Hz	1	1
0.2	6	2
0.4	2 (Respiration)	2
0.6	3	1
0.8	3	1
1.0	4 (Pulse)	1
2.0	1	2
	—	—
	20	13
	—	—
	Mean amplitude $\approx 300 \mu V$	Mean amplitude $\approx 1250 \mu V$

remained relatively constant. E.M.G. was repeated following a 6-week course of flavoxate hydrochloride (200 mg q.d.s.). Her urgency diminished and she has not had any retention. The main feature of her new low-frequency E.M.G. was absence of the build-up of activity prior to micturition.

Case 4. Patient D. M., aged 59. She has had urgency and stress incontinence for many years. No neurological abnormalities were noted. The urethral pressure profile was low. A cystometrogram revealed a bladder capacity

of only 125 ml with a residual of 70 ml. As far as the low-frequency detrusor E.M.G. was concerned, this small bladder was active with E.M.G. peak amplitudes of approximately 1 mV frequencies in the range 0.1 to 3 Hz (Table III). The activity continued before and during micturition without any marked build-up prior to micturition, but after micturition there was a marked drop in amplitude and a loss of the higher frequency components (1 to 5 Hz). Marked swings in the low-frequency detrusor E.M.G. occurred with fluctuations in the bladder pressure.

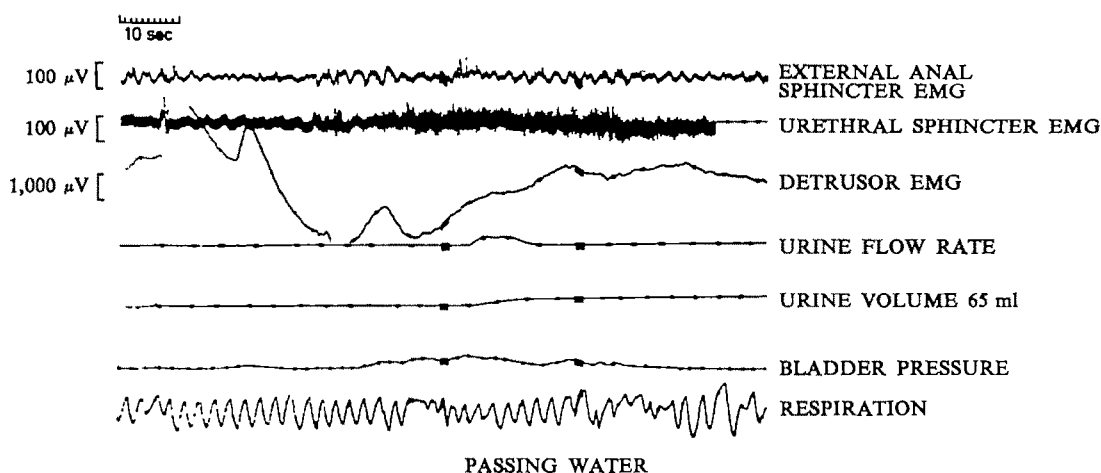


Fig. 4. Fluctuation in the low-frequency detrusor E.M.G. in a patient with disseminated sclerosis just prior to and during micturition.

Table III

Wave Analysis of the Low-frequency Detrusor E.M.G. of Patient D.M.

Frequency	Number of Waves in a 30-second Epoch	
	Just prior to micturition	Just after micturition
0.1 Hz	0	0
0.2	0	2
0.4	1 (Respiration)	3
0.6	7	0
0.8	1	0
1.0	9	4
2.0	20 (Pulse)	9
3.0	12	8
4.0	9	6
	59	32
	Mean amplitude $\approx 1250 \mu V$	Mean amplitude $\approx 300 \mu V$

Case 5. Patient E. F., aged 55. This patient was well until 1970, when she had a hysterectomy for prolapse. Since then she experiences urge incontinence. She has a normal urine flow but is not able to stop voiding. She does not know when her bladder is full and her bladder does not empty completely. Neurological examination was normal. The bladder capacity was 200 ml. Otherwise cystometry and the urethral pressure profile were normal. The low-frequency detrusor E.M.G. revealed that this small bladder was in a state of continuous E.M.G. activity. There were no marked swings before or during micturition. The observation substantiated the patient's comment that

her water "just came away". The wave count for the detrusor E.M.G. is given in Table IV. The patient was given an intramuscular injection of 50 mg of emeprium bromide. 45 minutes later the mean detrusor E.M.G. amplitude had been reduced from 825 μ V to 355 μ V and the activity was concentrated in the range 1 to 5 Hz. Following the injection, the patient did not micturate during the period of observation whereas prior to it she micturated spontaneously at regular intervals.

Table IV

Wave Analysis of the Low-frequency Detrusor E.M.G. of Patient E. F.

Frequency	Number of Waves in a 30-second Epoch	
	Just prior to micturition	45 minutes after 50 mg i.m. emeprium bromide
0.1 Hz	0	0
0.2	2 (Respiration)	0
0.4	7	5
0.6	4	2
0.8	0	0
1.0	13 (Pulse)	12
2.0	13	12
3.0	7	11
4.0	4	16
5.0	4	3
	54	61
	Mean amplitude $\approx 825 \mu$ V	Mean amplitude $\approx 355 \mu$ V

Case 6. Patient D. L., aged 43. 13 months ago she noticed symptoms of urgency, nocturnal frequency and stress incontinence. A vaginal hysterectomy and repair were performed but without relief. She was overweight, her nervous system was normal and per vaginam there was a demonstrable stress incontinence and significant prolapse. A urethral pressure profile and cystometrogram was normal. A micturating cystometrogram showed good voluntary control but poor urethral milkback. No incontinence could be demonstrated.

Figure 5(a) shows her high frequency (spike) detrusor E.M.G. obtained during active micturition and whilst dribbling urine (Fig. 5(b)). Figure 5(c) shows the low-frequency (wave) E.M.G. with the patient sitting quite still.

Discussion

Almost 18 years have elapsed since any major study of the electromyographic activity of the mammalian urinary bladder has been published. Corey *et al.* (1951) and Boyce (1952) obtained low-frequency and Franksson and Peterson (1953) obtained high-frequency E.M.G. recordings by introducing twin electrodes via a cystoscopic carrier in the urethra and inserting them into the lateral bladder walls, sometimes under direct vision and sometimes blind. These manoeuvres were repeated by one of us (S. L. S.) but it was found impossible to place and retain electrodes within the detrusor muscle with any consistency. Because of this difficulty it was decided to attempt the trans-vaginal approach. This route had the additional advantage of positioning the electrodes in the trigone and basal zones, which by the isolated strip technique have been shown to possess the most low-frequency E.M.G. activity (Corey and Vest, 1954). The patient can subsequently move from the examination couch to the commode without the electrodes becoming detached. No evidence of soft tissue or urinary tract infection has been detected in our patients following the investigations. Because of the work of Bates (1971) and others who have recorded multiple parameters in the assessment of bladder function it was felt necessary to record simultaneous intravesical and rectal pressures and urine flow rates and volume. It has proved valuable

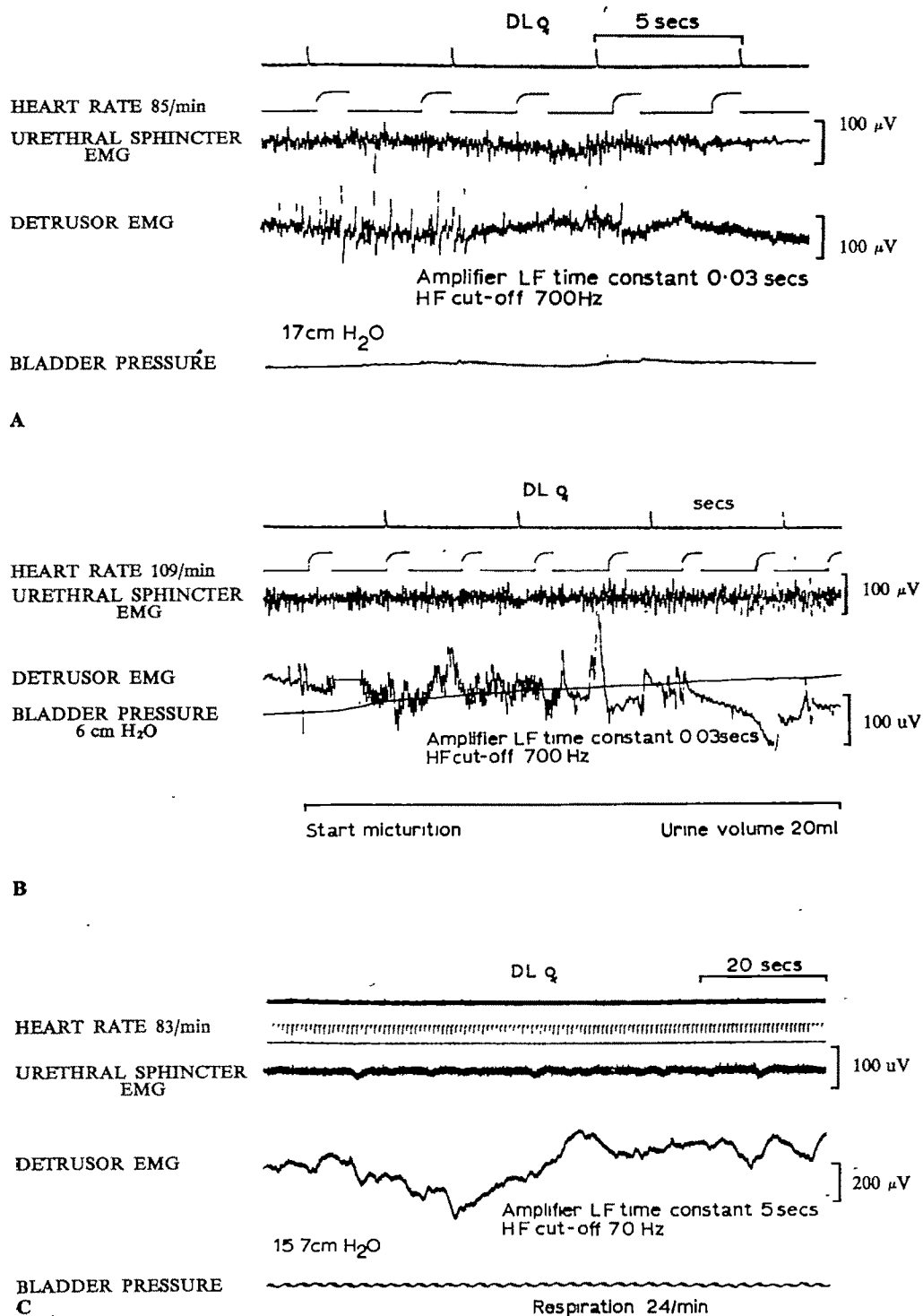


Fig. 5. High-frequency (spike) detrusor E.M.G. activity A, before, B, during micturition, C, low-frequency (wave) detrusor E.M.G.

to record simultaneously the activity of the urethral sphincter and the bladder pressure. By this means it is possible to detect the detrusor-sphincter imbalance which can accompany neuropathic bladder disorder (Boyarsky, 1967).

From the case histories presented it is apparent that, as suggested by Corey *et al.* (1951) and Boyce (1952), the low-frequency detrusor muscle E.M.G. does have a useful part to play in the diagnosis of detrusor dysfunction. For a normal bladder, Boyce found a regular E.M.G. pattern of approximately 2.4 waves per minute (0.04 Hz) with an amplitude of approximately 650 μ V. He was able to show diminished and increased low-frequency E.M.G. activity in hypoactive and hyperactive bladders, and that similar spontaneous electrical activity was detectable in animal bladders. We have been able to show similar low-frequency detrusor E.M.G. patterns *in vivo* in dogs and *in vitro* in guinea-pig, rabbit and human bladders. Unlike Boyce, our waveforms were not bi-phasic, but were of a random nature similar to an electroencephalogram. This

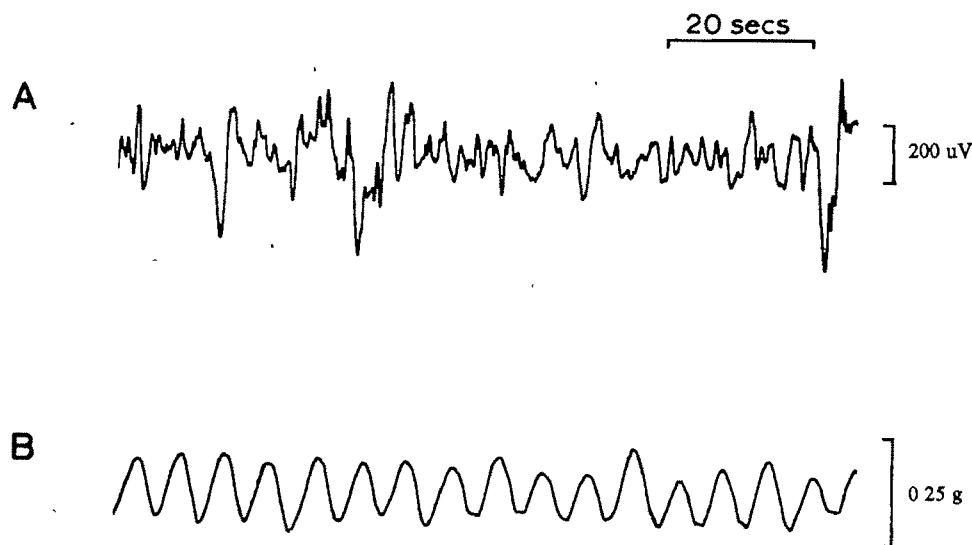


Fig. 6. A, Low-frequency E.M.G. activity of a strip of human bladder suspended in an organ bath without stirring. B, Spontaneous mechanical activity of human bladder strip.

difference may be due to the longer low-frequency time constant in our recorder. The appearance of marked low-frequency detrusor E.M.G. activity seems to be related to the desire to micturate. It has been clearly demonstrated that in a normal bladder this activity is minimal when the subject is relaxed and without any desire to micturate. In patients with upper motor neurone lesions, the build-up of low-frequency detrusor activity prior to micturition can be quite striking. The effect of anti-spasmodic drugs in reducing the low-frequency detrusor E.M.G. amplitude and swings has been demonstrated and this is related to a diminution of the patient's desire to micturate. The spike activity of the detrusor E.M.G. is particularly related to the act of micturition.

Movement artefacts generated by the patient and appearing on the detrusor E.M.G. recording were readily distinguished by their transient character. It is interesting to note that similar low-frequency E.M.G. signals were obtained from isolated strips of animal and human bladders where there was no unwanted movement (Fig. 6).

With regard to the high-frequency (spike) components of the detrusor E.M.G., our findings agree broadly with those of Franksson and Peterson (1953). We have observed bursts of activity (50 μ V) with a duration of 0.5 to 3 seconds appearing at random intervals of between 1 and 15 seconds whilst the patient was sitting before micturition. As the bladder pressure commenced to rise just prior to micturition larger amplitude spikes (100 to 150 μ V) appeared. These appeared

at about 0.05 second intervals in bursts until micturition ceased and the normal high-frequency detrusor E.M.G. returned. In a patient with a highly irritable bladder, there was a continuous spike and wave activity covering the range 0.8 to 15 Hz with no obvious change during micturition.

Our technique can conveniently be applied to female out-patients and so far we have investigated the detrusor E.M.G. of 22 patients. We are now storing the various signals on magnetic tape and playing this into a digital computer system for the purpose of cross-correlation and frequency analysis.

It is also our intention to examine further the relationships existing between the high- and low-frequency components of detrusor E.M.G. and bladder pressure and volume.

The study of the detrusor muscle E.M.G. should help to identify patients with uninhibited detrusor function and guide the choice and administration of anti-spasmodic drugs or surgery.

Summary

A technique is described for investigating in conscious female patients both the low-frequency (wave) and high-frequency (spike) components of the detrusor E.M.G.

The low-frequency component appears to be of value in assessing the chemotherapy by anti-spasmodic drugs in urgency of micturition.

It is a pleasure to acknowledge the help of Mr Kenneth Wallace, Senior Technician; Sisters Rich, Meehan and Prince of the Incontinence Clinic at the Shaftesbury Hospital and the financial support of the Board of Governors of the St Peter's Group of Hospitals. The Medical Research Council kindly provided the digital computer facilities.

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Transection of the Bladder with Particular Reference to Enuresis

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The basic cause in the central nervous system of defective inhibition of bladder activity can only rarely be removed. Palliative suppression of the resulting frequency, urgency and incontinence by anticholinergic drugs such as propantheline or imipramine is usually inadequate in severe cases, and may have to be continued indefinitely. Palliative treatment by surgery depends on 2 principles—denervation or replacement of the over-active bladder muscle.

The effect of denervation of the bladder by section of the pelvic splanchnic nerves in the female is inconsistent and produces severe constipation (Gibbon, 1967); in the male it might result in impotence. Excision and replacement of the detrusor by entero-cystoplasty is a rational procedure, but seems excessively major when the bladder itself is healthy.

Selective denervation of the detrusor as described in 1967 by Turner-Warwick and Ashken—under the title of “Supratrigonal Denervation: Cystocystoplasty”—would appear to be the ideal operative treatment for such cases. The rationale of this procedure is that nerve fibres to the detrusor enter the bladder about the level of the inferior vesical arteries and thence spread upwards into the detrusor, so that circumferential division of the bladder just above the level of the entry of the ureters disrupts the nerve supply to the detrusor leaving the sensory supply of the bladder base intact. Turner-Warwick and Ashken combined this transection “with division of all inferior lateral communications including the inferior vesical vessels”. The blood supply from the superior vesical arteries to the denervated area was left undisturbed.

This type of operation—but confined to the transection of the bladder—seems to have been first applied in the treatment of the enuretic syndrome¹ in 1969 (Yeates, 1970). The results in the first 2 cases were so satisfactory that it seemed justified to discuss the procedure with adult patients seen subsequently whose symptoms were severe and which showed no signs of abating.

In addition, the operation has been used in the treatment of interstitial cystitis so that the patient could allow the bladder to distend without the production of pain (Worth and Turner-Warwick, 1973).

Patients and Method

The series of patients comprised: 14 with the enuretic syndrome, 1 with similar lifelong day symptoms but without nocturnal incontinence; 1 with multiple sclerosis, 2 with interstitial cystitis, and 1 with symptoms of doubtful origin.

The enuretic cases were selected by the following criteria:

- (i) The failure to obtain an acceptable response from medical—often including psychiatric—treatment.
- (ii) The absence of any detectable urological abnormality, preferably with a normal bladder capacity under general anaesthesia, in contrast to the reduced functional capacity when not under anaesthesia.

¹ In this paper “enuresis” is used to indicate nocturnal incontinence of functional origin existing since childhood. “Enuretic syndrome” is applied to those patients who have in addition deficiency of inhibition of bladder activity by day.

- (iii) Diurnal symptoms of frequency and urgency to a degree of inconvenience that made the patient willing to be subjected to what was described as an experimental major operation.

Similar criteria were applied to the case of apparently congenital defective inhibition, and to the case of multiple sclerosis.

Only simple cystometry with the patient supine was carried out. It was usually most unhelpful, merely confirming an increase in bladder irritability by the early onset of the desire to void and exceptionally an uninhibited bladder contraction.

Procedure

The few patients with symptoms and objective evidence of bladder outlet obstruction in addition to the enuretic syndrome were treated first by transurethral resection.

Although we perform the preliminary steps and final drainage slightly differently we both use the same basic technique, viz. a complete full-thickness transection of the bladder wall 2 cm above the bladder neck anteriorly and 2 cm above the ureteric orifices and inter-ureteric bar by a transvesical approach.

Ureteric catheters are passed either endoscopically or after the bladder is opened for easy identification of the juxtavesical parts of the ureters. These are subsequently fixed to the trigone by fine sutures to prevent their being extruded during the operation.

The bladder is exposed through a Pfannenstiel or vertical incision and freed as widely as possible by blunt dissection from the pelvis as in the preliminary stages of retropubic prostatectomy. Division of the detrusor is begun either by a transverse incision across the anterior wall (DME) or by a vertical incision which is extended down to this level before continuing the section laterally (WKY) (Fig. 1). The division above the trigone is carried out from within the bladder with dissecting forceps and scissors into the extravesical plane which is easily recognised. The posterior and lateral lines of section are subsequently joined above the ureteric orifices, the juxtavesical part of the ureter (easily identified by its contained catheter) being displaced downwards and backwards. Complete separation of the 2 parts is ensured by stripping the bladder upwards for about 1 cm from the underlying tissues and dividing any remaining connecting strands.

The sutures retaining the ureteric catheters are removed and the catheters withdrawn.

The bladder is then reconstructed using a single layer of continuous 2/0 chromic catgut avoiding the mucosa. Each suture line is begun in the midline posteriorly. Where the original bladder incision had begun as a vertical anterior incision the suture is merely carried up the latter at the end of the closure. The bladder is drained by either only a Foley catheter per urethram or in addition a suprapubic tube which is left in for 3 days. Extravesical tissue drainage is supplied. The urethral catheter drainage is maintained for 7 to 10 days.

During the postoperative course bladder discomfort was notably absent in spite of the presence of the catheter. (The outstanding exception was the patient J. E. R. who had a persistent desire to void until the catheter was removed.)

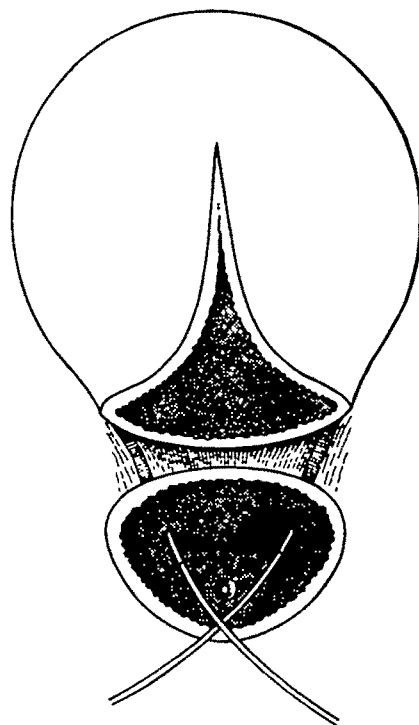


Fig. 1. Transection of the bladder commencing with a vertical incision. Ureteric catheters retained by fine sutures.

Following removal of the catheter there was usually frequency and urgency with nocturnal incontinence for the first 24 to 48 hours, but thereafter there was nearly always rapid improvement so that by about the 3rd day there was usually no urgency and the frequency was often completely normal for the first time in the patient's life. Very exceptionally the bladder irritability took up to 7 days to improve.

Case Reports

Enuretic Syndrome

Mr R. M. D.O.B. 13.6.38. 18.3.64: Enuresis and diurnal 1 to 2-hourly frequency and urgency with potential precipitancy all his life. Stream always slow. Father enuretic until death at age 45. No residual urine. Slight trabeculation of bladder. 21.8.64: T.U.R. bladder neck. Temporary marked improvement for some months. Emigrated to Canada. 1965: recurrence of all symptoms. 1969: returned to Britain. Investigations negative. Bladder capacity under G.A. 450 ml. 29.7.69: *Denervation*. No recurrence of frequency or urgency since operation. 6.10.72: No day symptoms. Occasional nocturnal incontinence.

Mr H. C. D.O.B. 14.5.26. 8.1.68: Enuresis and diurnal 1 to 2-hourly frequency and urgency all his life. No residual urine. Bladder capacity under G.A. 540 ml. 28.1.69: *Denervation*. Immediate improvement in urgency, frequency 4-hourly. Occasionally slightly damp at night. 3.3.69: Cystogram. Symptomless free right ureteric reflux. 13.4.70: No day symptoms. Nocturnal incontinence about once in 6 weeks. I.V.P.-n.a.d. Very small amount of residual urine.

Mrs M. D. D.O.B. 25.2.40. 2.8.67: Enuresis and 2 to 3 hourly diurnal frequency and urge incontinence all her life. Daughter aged 9 is persistent enuretic with diurnal urgency. Investigations showed a low-grade bladder trabeculation and some mucosal thickening with polypi at the bladder neck. Bladder capacity under G.A. 450 ml. No residual urine. 13.8.68: T.U.R. bladder neck. Definite temporary improvement in urgency but enuresis unchanged. 12.6.70: *Denervation*. Immediate marked improvement which has been maintained. 15.1.73: Normal diurnal frequency. No urgency. Enuretic averaging once a week.

Miss Y. R. D.O.B. 26.9.39. 8.12.69: Enuretic with diurnal urgency and frequency all her life. Sister and brother had been enuretic until the age of 14. Niece aged 13 still enuretic. Bladder capacity under G.A. 630 ml. 9.10.70: *Denervation*. Symptom free both day and night until April 1971 since when enuretic about twice a week. 31.5.72: I.S.Q. Cystoscopy showed "residual urine" 30 ml. Capacity 600 ml. Healthy bladder. Circumferential scar easily seen as thin white line.

Mr G. G. B. D.O.B. 8.8.42. 21.4.71: Enuresis until age 8. Residual 1-hourly frequency and urgency. Capacity under G.A. 350 ml. 19.10.71: *Denervation*. 15.1.73: Symptom free night and day.

Mr D. E. W. D.O.B. 15.10.47. 12.7.71: Persistent enuresis until aged 13. Occasionally enuretic since. No day symptoms until 1 year before seen, since when 2-hourly frequency and urgency. Bladder capacity under G.A. 460 ml. 18.1.72: *Denervation*. 11.1.73: Symptom free night and day.

Mr K. H. D.O.B. 12.5.46. 26.12.67: Enuretic with diurnal frequency and urgency all his life. Brother enuretic until age 16. Bladder capacity under G.A. 500 ml. Attempted suicide "because engagement broken on account of enuresis". 14.3.72: *Denervation*. 25.10.73: Symptom free by day. No enuresis unless he has heavy alcohol intake before retiring. 16.1.73: No enuresis. Frequency 3 to 4-hourly. Sometimes urgency but no incontinence.

Mr M. J. H. D.O.B. 8.8.48. 3.11.69: Enuretic till age 11. Residual diurnal 1-hourly frequency and urgency. Bladder capacity under G.A. 450 ml. 25.5.72 *Denervation*. 12.1.73: Frequency 3-hourly, no urgency (no night symptoms).

Mr I. L. D.O.B. 14.7.46. 12.10.71: Nocturnal enuresis all his life with diurnal frequency and potential urge incontinence especially after drinking beer. Bladder capacity under G.A. 350 ml. 26.9.72. *Denervation*. 17.1.73: Symptom free night and day. Frequency at least 6-hourly with no urgency.

Miss D. E. D.O.B. 12.3.54. 5.4.71: Nocturnal enuresis since birth with 2-hourly frequency and urgency during the day. Also giggling incontinence dysfunction. Capacity under G.A. 380 ml. 30.6.72: *Denervation*. 14.8.72: Enuretic only once in previous month. Diurnal frequency up to 5-hourly with no urgency. 20.11.72: Awakened during the night with great urgency with recurrence of nocturnal incontinence every night for 10 days, but subsequently became completely symptom free on holiday. 15.1.73: Enuretic 2 weeks per month. Frequency 2 to 3-hourly. No urgency.

Mr D. C. D.O.B. 3.5.48. 9.8.71: Patient first seen with symptoms almost identical to Mr J. C. Treatment and response identical. 4.1.72: T.U.R. bladder neck. 12.4.72: *Denervation*. 20.12.72: Symptom free night and day. No residual urine.

Mr A. M. D.O.B. 15.11.48. 3.6.71: Lifelong enuretic. Diurnal frequency, urgency and incontinence. Attempted suicide because of enuresis. Bladder capacity under G.A. over 500 ml. 19.8.71: *Denervation*. Complete relief of symptoms for 3 months then return of enuresis and diurnal frequency though less than before operation. 5.6.72: Cystogram normal. 60 ml residual urine. Bladder capacity 350 ml awake. 800 ml under G.A. 10.9.72: *Denervation repeated*. 4.12.72: Enuresis unchanged but no symptoms by day. Disipidin snuff at night 1 to 2 a week. 2.1.73: No further enuresis. 25.4.73. Symptom free for 4 months. No therapy.

Mr A. H. D.O.B. 27.9.45. 13.11.71: Enuretic till age 8 with recurrence of nocturnal enuresis in year before seen. Diurnal hesitancy, poor stream, urgency and frequency all his life. Trabeculated bladder with hypertrophied bladder neck. Functional bladder capacity 150 ml awake. 450 ml under G.A. 6.3.72: T.U.R. bladder neck. Frequency and enuresis unchanged. 9.5.72: *Denervation*. 11.12.72 Diurnal symptoms somewhat improved. Enuresis unchanged. Probably strong psychological element. Functional bladder capacity 400 ml awake. 450 ml under G.A.

Mr R. M. Age: 31. Enuresis. Hesitancy, poor stream, frequency, urgency. Capacity 250 ml under G.A. 150 ml when conscious. Hypertrophied bladder neck trabeculated bladder. T.U.R. 2.4.72: Stream improved, no hesitancy. *Denervation* 8.11.72: 1.2.73: Symptom free day and night.

Hypertonic Bladder of Unknown Aetiology. No Nocturnal Incontinence

Mr R. L. D.O.B. 14.6.29. 6.7.68: $\frac{1}{2}$ - to 1-hourly frequency and urgency all his life. Poor stream. Marked trabeculation with hypertrophy of bladder neck. 21.11.68: T.U.R. bladder neck. Flow improved. Frequency I.S.Q. 14.6.72: *Denervation*. 4.12.72: Normal frequency. No urgency. No residual urine.

Multiple Sclerosis

Mrs J. S. D.O.B. 3.11.28. 15.2.70: Multiple sclerosis 10 years. Paraplegic. 1- to $\frac{1}{2}$ -hourly frequency with urge incontinence and nocturnal incontinence. Cystometry: urgency at 50 ml. No residual urine. Capacity under G.A. 400 ml. 1970-71—urethral dilatations to 45F and probanthine. Successful initially, latterly ineffective. 10.1.72: *Denervation*. 13.12.72: Frequency 2-hourly. Can postpone for 10 minutes when desire to void becomes uncontrollable. Functional capacity increased to 450 ml. Complete emptying. No further incontinence night or day.

Interstitial Cystitis

Mrs A. S. D.O.B. 14.7.18. 16.6.69: Urgency, frequency and dysuria. Typical interstitial cystitis. Bladder capacity under G.A. 300 ml. 1969-70—repeated dilatation of bladder effective at first. No response to steroids. Bladder capacity reduced to 180 ml. under G.A. 14. 6.71: *Denervation*. Immediate relief of bladder pain on recovery from anaesthetic. Total relief of symptoms until May 1972. Bladder capacity increased to 350 ml. January, 1972: left hemiplegia. 15.1.72: Gradual return of frequency, urgency and incontinence, during the last 6 months. No response to medical treatment. No dysuria. Capacity remains 350 ml.

Mrs N. H. D.O.B. 7.9.05. 15.5.67: 1 year progressive frequency. Then hourly night and day with pain in back on postponing micturition. Typical interstitial cystitis. Capacity under G.A. 300 ml. Temporary slight response to distension of bladder and inadequate response to steroids. Frequency persisted 2-hourly with pain on distension. Capacity under G.A. remained about 300 ml. 24.11.72: *Denervation*. Immediate relief of distension pain. 8.1.73: Frequency 3-hourly night and day. No distension pain. Urine clear.

Unknown Aetiology

Mr J. E. R. D.O.B. 22.4.29. 1952: Left renal tuberculosis with severe cystitis. Antituberculous therapy with left nephro-ureterectomy. Persistent frequency 1-hourly during the day with 3-hourly at night since. February 1970: No evidence of urinary tuberculosis. Residual calcification in prostate. Bladder capacity under G.A. 250 ml. No sign of ulceration. 15.7.71: T.U.R. prostate. No benefit. Histology of prostate showed no inflammatory changes. 30.11.71: Cystoscopy showed mild chronic congestion of the trigone and prostatic urethra. *Denervation*. No benefit. 15.3.72: Frequency $\frac{1}{2}$ -hourly during the day, 3 times at night, yet denies urgency. Urine normal. Again negative for T.B. on guinea-pig inoculation. 17.1.73: Symptoms unchanged. States he has been impotent since denervation but has erections on non-sexual occasions. Referred for psychiatric opinion.

The cases are summarised in the Table.

Table

Showing Principal Features of Patients with the Enuretic Syndrome

Patient	Sex	Age	Enuresis		Day Symptoms		Comment on Results		Length of Follow-up (years)
			Pre-op.	Postop.	Pre-op.	Postop.	Night	Day	
R. M.	M	31	Every night	Occasional	F 2-hourly U+++ I+	F Normal U- I-	V. good	Excellent	3 3/12
M. D.	F	30	Every night	Once weekly	F 2- to 3-hourly U+++ I+	F Normal U- I-	Good	Excellent	2 6/12
Y. R.	F	31	Every night	None for 6/12 then twice weekly	F 1½ hours U- I-	F Normal U- I-	Improved	Excellent	1 7/12
H. C.	M	43	Every night	Occasional	F ¼- to 2-hourly U++ I+	F 4-hourly U- I-	V. good	V. good	1 3/12
A. M.	M	25	Every night	None for 3/12. Repeated denervation	F 1- to 2-hourly U+++ I+	F normal U- I-	Now good	Excellent	1 3/12
G. G. B.	M	29	Until age 8	None	F 1-hourly U++ I-	F Normal U- I-	—	Excellent	1 3/12
D. E. W.	M	26	Occasional	None	F 2-hourly U++ I+	F Normal U- I-	Excellent	Excellent	1
J. C.	M	26	Most nights	None	F 1- to 2-hourly U+++ I+	F Normal U- I-	Excellent	Excellent	1
M. J. H.	M	25	Until age 11	None	1-hourly U++ I-	F 3-hourly U- I-	—	Good	8/12
D. C.	M	24	Most nights	None	F 1- to 2-hourly U+++ I+	F Normal U- I+	Excellent	Excellent	8/12
A. H.	M	27	To age 8 for 1 year from age 26	Unchanged	F 2-3 hours U++ I-	Improved	Poor	Improved	7/12
D. E.	F	18	Nearly every night	2 weeks/month	F 2-hourly U 2-hourly I+	F 2-hourly, otherwise normal U- I-	Improved	Good	7/12
R. L.	M	43	None	None	F ¼- to 1-hourly U++ I-	F Normal U- I-	—	Excellent	6/12
R. M.	M	31	Most nights	Dry	F 2-3 hours U++ I-	F Normal U- I-	Excellent	Excellent	3/12
K. H.	M	26	Nearly every night	None unless he drinks++ at night	F+ U+	F Normal U- I-	Good	Good	3/12

F = Frequency (approximate average). U = Urgency (Intensity as described by patients). I = Incontinence.

Comments

The postoperative bladder irritability immediately on removing the catheter was presumed to be due to oedema and contraction of the denervated bladder vault.

Diurnal Function. The desire to void appeared to be quite unaffected by the procedure except that its frequency was reduced. Urgency was almost always completely relieved and the time between acts of micturition greatly improved usually to nearly normal.

Some patients had to initiate micturition by straining, but this was remarkably inconstant, most patients stating that the whole act of micturition was quite normal with a feeling of complete bladder emptying. This was confirmed on observation and investigation. In most cases postoperatively there was no residual urine and when present this was never more than 30 ml.

Nocturnal Function. The original primary objective was to treat the diurnal frequency and urgency, but hoping as a bonus that the increased functional bladder capacity would accommodate a nocturnal output of urine without setting up a detrusor contraction, and so also prevent the nocturnal incontinence. The frequency of nocturnal incontinence was, in fact, reduced to a variable but nearly always to a useful degree.

Simple cystometry some weeks after operation constantly showed a bladder capacity almost the same as that found under general anaesthesia before operation. The desire to void was delayed until this capacity was reached. No contraction waves were demonstrated in the supine position, but on removing the catheter the patient was able to empty the bladder standing or sitting without difficulty or detectable straining.

The best results by far were in patients without detectable organic abnormality either locally or in the nervous system.

The worst result was in the patient J. E. R., who might have had a source of afferent stimulation from the trigone or prostate, though this was in fact unproved. At least some of this patient's symptoms appeared to be psychogenic. In retrospect, this operation was ill-advised and we would regard the presence of trigonitis or prostatitis as a definite contra-indication to the procedure.

The 2 cases of interstitial cystitis were benefited considerably though in one the follow-up is short, and in the other urgency returned after a cerebral thrombosis, though it might be thought that the operation would have prevented the effects of decreased inhibition of bladder activity.

The development of reflux in the case H. C. was presumably due to the incision being too near to a ureteric orifice resulting in division of the bladder muscle fibres partly concerned in its prevention (Castro and Fine, 1969).

Many questions, such as the lack of interference with what appears to be normal micturition in most cases from almost immediately after operation, remain to be answered by more detailed investigation.

Conclusions

Our experience with this operation to date seems to justify its further use in cases of enuresis with diurnal urgency persisting into adult life, and perhaps there is a case for performing it at about age 16 which is the view of many of our patients.

The value of the procedure in other cases with defective inhibition or excessive stimulation from the vault (as in interstitial cystitis) is less certain but is obviously worthy of trial in selected cases.

The cases were selected without detailed cystometric investigation. The results clearly indicate that such investigation is not essential but presumably it might make the selection more accurate in doubtful cases.

Summary

15 adults with life-long urgency, and usually enuresis, were treated by supratrigonal denervation of the bladder by full thickness transection.

The improvement in day symptoms was judged "excellent" or "very good" in 11, "good" in 3 and "improved" in 1.

Nocturnal incontinence was reduced considerably in all except 1.

The results seem to be good enough to warrant its further use in nocturnal enuresis with diurnal symptoms.

Other selected cases with deficient inhibition or excessive stimulation from the bladder vault (e.g. interstitial cystitis) have shown sufficiently encouraging results to justify its further trial in these.

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Transection of the Bladder for Adult Enuresis and Allied Conditions

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There has been scant reference in the literature to the surgical treatment of the adult enuretic. These patients are predominantly males with a lifelong history of diurnal frequency and urgency to the extent of incontinence, although occasionally similar symptoms develop later in life as a result of disease of the central nervous system. They have usually run the gauntlet of polypharmacy and night alarms to no avail and rely on penile appliances and waterproof sheeting.

Marshall (1954) carried out partial sacral parasympathectomy by the abdominal route in 5 adult enuretics, but this operation is difficult and in males impotence may result. Division of the parasympathetics by the parasacral approach of Thiermann (1953) is much simpler but has proved unsuccessful in 2 of our female patients (Gibbon, 1967). Miller (1966) claimed some success from bladder neck resection but this may induce infertility in the young male.

Enterocystoplasty (Gibbon, 1967; Angell, 1969; Hickinbotham, 1971), by enlarging the capacity of the bladder, has gratifying results but is a major procedure and may result in incomplete bladder emptying.

Turner-Warwick and Ashken (1967) have described "supra-trigonal denervation" for hyper-sensitive bladders. A modification of this operation for the treatment of enuresis was reported by Yeates (1970). We describe 7 patients treated by this latter method.

Patients and Procedures

There were 7 patients with enuresis: 2 women and 5 men.

The selection of patients was based on clinical assessment. Each patient gave a history of urgency and urge incontinence. Neurological abnormalities were excluded by clinical examination. Urinary infection was excluded. An intravenous pyelogram sometimes showed trabeculation of the bladder which was confirmed at cystoscopy, when bladder neck hypertrophy, due to thickening of the lower edge of the overactive detrusor, was often found.

Cystometrograms were carried out on some of these patients but have been of limited help in the selection of cases for operation. We believe that the bladder capacity measured under general anaesthesia should be within normal limits and that there should be no evidence of outflow obstruction.

Technique

The bladder is exposed through a Pfannenstiel incision and opened anteriorly just above the bladder neck with a transverse incision which is carried completely around the bladder just above the trigone. Care is taken not to injure the ureters posteriorly. The blood supply to the dome of the bladder by the superior vesical arteries is left intact and there is minimal disturbance of the inferior pedicles. The bladder is resutured with catgut, and then drained by a urethral catheter for a few days (Fig. 1). Some patients have had a slight modification of the operation as explained in the case histories below.

Case Reports

Case 1. S. C. Woman, aged 24 years. She was enuretic until 15 years old and presented with an 18-month history of urgency and frequency. The frequency was every 10 minutes by day and 1-hourly during the night. There was no incontinence. The operation of bladder transection was performed a year ago. In this particular patient a small bridge of bladder tissue was left intact overlying the ureters on each side. At the present time her frequency and urgency are much improved; she has no nocturnal frequency and voids 2-hourly during the day. A cystometrogram before operation showed a grossly hypertonic bladder (*i.e.* intrinsic detrusor pressure above 25 cm water); its maximum capacity was 200 ml. Now her maximum capacity is 400 ml., a rise in bladder pressure occurring above 300 ml with a shift to the right of the cystometrogram curve.

Case 2. R. T. Male, aged 19 years. This man presented with lifelong enuresis and frequency during the day. Bladder transection was performed 4 months ago. Now he is dry during the night and he regards the operation as "a complete success". The bladder capacity before operation was 300 ml with a hypertonic curve above 100 ml; the capacity is now 425 ml, high pressures only developing above 200 ml.

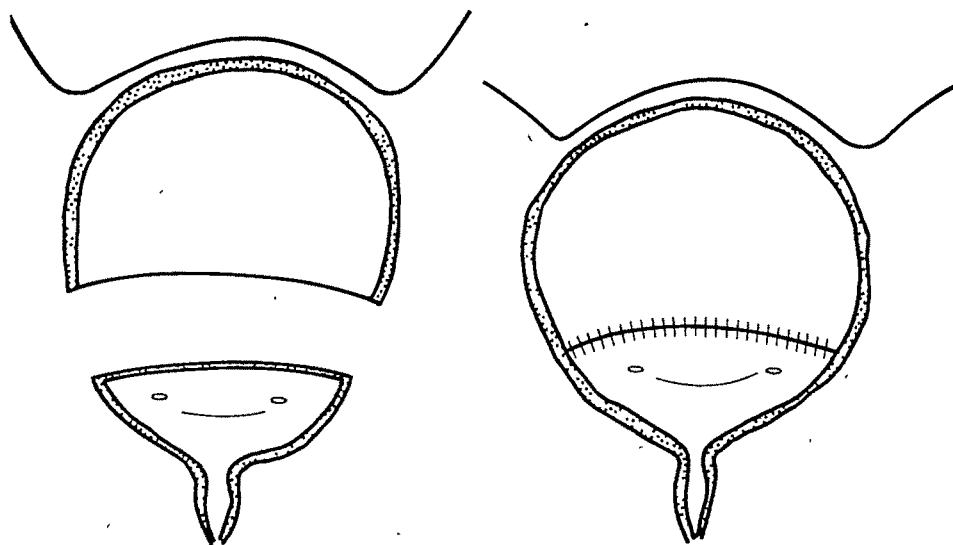


Fig. 1. Diagram to show the level of transection of the bladder. In some patients a bridge of tissue was left intact over the ureters.

Case 3. J. W. Man, aged 22 years. He was enuretic until the age of 17 years. He came with a 4-year history of urge incontinence. Despite voluntary fluid restrictions his frequency was hourly by day and twice at night. Bladder transection was performed 7 months ago. At present he does not need fluid restriction and is rarely incontinent. His urgency is reduced in severity and his capacity has improved as reflected by a reduced frequency of micturition of hourly by day and once at night. Prior to complete bladder transection the bladder capacity was 360 ml, uninhibited contractions occurring at 300 ml; now the capacity is 500 ml with only a mild hypertonic curve present at full volume.

Case 4. F. B. Man, aged 25 years. He was never enuretic but presented with urge incontinence of 2 years' duration, passing urine hourly by day, twice at night, and needed pads to keep dry. A subtotal bladder transection was done in a similar manner to the first patient, a bridge of tissue remaining above each ureter. Now he states "this is the best thing that could have happened to me", he is free of urgency and incontinence, and passes urine every 3 hours during the day and seldom by night. Before operation the bladder capacity was 600 ml with high pressure developing above 100 ml. A shift to the right is now seen, the bladder capacity is unaltered but a high pressure is only found after the bladder is filled above 350 ml.

Case 5. M. F. Man, aged 25 years. He was enuretic until the age of 12 years and presented with a 4-year history of incontinence, passing urine at least 1-hourly by day and twice by night and wet beds were commonplace. A self-

imposed fluid restriction had not lessened his symptoms. Six months ago a subtotal bladder transection was performed, the bladder being completely divided anteriorly from ureter to ureter with an intact bridge of muscle posteriorly between the ureters. Since then incontinence is a rarity and his capacity appears subjectively improved although the urgency and frequency are still troublesome. The pre-operative bladder capacity was 200 ml, an uninhibited series of contractions developed at volumes greater than 100 ml. Following operation the capacity is unchanged, but high pressures are found only at full capacity resulting in voiding.

Case 6. D. P. Man, aged 29 years. He was a lifelong enuretic presenting with a 3-year history of urge incontinence, passing urine 1-hourly by day and 4 times each night. He was found to have an atrophic kidney with the ureter opening into the right vas deferens. The kidney and ureter were removed and bladder transection performed, a bridge being left in the left posterior quadrant of the bladder wall. A great improvement was noted at first, but recently urge incontinence and enuresis have recurred, although an improved ability to delay voiding and an increased bladder capacity are claimed by the patient. His bladder capacity before surgery was 160 ml, uninhibited contractions occurring above 50 ml; now the capacity is 300 ml; contractions occur above 150 ml.

Case 7. P. G. Woman, aged 29 years. She had lifelong enuresis together with a 2-year history of urge incontinence, passing urine hourly day and night and needing pads to keep her dry. A complete bladder transection was performed 2 months ago. She was symptom free until 2 weeks ago when her urgency and enuresis recurred. However, the frequency has improved, now being 2-hourly by day and 4 times by night. Despite her urgency she can delay micturition for several minutes. The pre-operative bladder capacity was below 100 ml, a high-pressure uninhibited contraction occurred immediately on filling. Now her capacity is 200 ml and contractions develop above 100 ml.

In summary, 2 of these patients were completely cured of their symptoms, but all showed some degree of subjective improvement. Cystometrograms demonstrate an increased bladder capacity with a shift to the right in all patients. The postoperative flow rates were all within the normal range (*i.e.* 14 ml/sec and above). The bladder pressure waves ranging from 20 to 50 cm of water were confirmed by separate simultaneous pressure recordings of the rectal and bladder pressures to be of detrusor origin.

Comments

The operation of bladder transection may be a useful technique in the management of persistent enuresis, or in cases of uninhibited detrusor action. At present we do not know if it is the incidental division of some of the nerves of the bladder, or the interruption of the muscular integrity of the detrusor which is of prime importance. In this connection the technique used in our operations and the normal detrusor activity postoperatively strongly suggest that denervation has not been a significant factor in these cases. On the other hand the constant shift of the cystometrogram curve to the right after surgery makes it unlikely that the whole effect is a psychological one.

Mahoney (1972) has described a technique of multiple detrusor myotomy which proved effective in dealing with a hypercontractile bladder in a 4½-year-old girl. This consisted of a series of incisions from one side of the bladder to the other, vertically as well as transversely, dividing the muscle but leaving the mucosa intact. This procedure would probably have the same effect as transection.

Summary

Seven patients with enuresis and diurnal urgency frequency and sometimes incontinence were treated by transection of the bladder.

Two of the patients were completely cured of their symptoms. All showed some degree of subjective improvement.

Cystometry showed that the operation did not prevent contraction of the detrusor, suggesting that denervation has not been a significant factor.

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INTERNATIONAL BLADDER CANCER CONFERENCE LEEDS, 22nd to 24th September 1971

President: Professor L. N. Pyrah, Leeds

Chairmen: Dr J. Higginson, Lyon, France
Professor P. N. Magee, London
Dr F. K. Mostofi, Washington, D.C., USA
Mr D. M. Wallace, London
Dr W. F. Whitmore, New York, N.Y., USA

Report on International Bladder Cancer Conference —Leeds 1971

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An international conference on bladder cancer was held in Leeds in September 1971 under the auspices of the International Union against cancer (U.I.C.C.) and with other sponsors. The conference discussed the biology, epidemiology, chemistry and pathology of bladder cancer, its clinical management and some aspects of clinical research. This summary is not in any way intended to be comprehensive but merely to highlight some of the topics which were felt to be relevant to the clinician. A summary of the papers of a more purely scientific nature has already been published in the *European Journal of Cancer* (1972).

Epidemiology and Aetiology

Higginson (World Health Organisation, Lyon) discussed the epidemiology of bladder cancer and observed that there has been an increased incidence over the last 2 decades in the United States and in Europe. While this may be due partly to modifications in methods of registration, it is almost certainly a true increase for most countries.

Bengtsson, Angervall, Johansson and Walqvist (University of Gothenburg) described an increased incidence of tumours of the renal pelvis in relation to the abuse of drugs containing phenacetin, but no increase in bladder tumours. The average yearly incidence of carcinoma of the renal pelvis in Sweden is 1 case per 183,000 inhabitants. However, in a clinical study of analgesic nephropathy in which 104 patients were followed over an average of 5.3 years, 9 patients developed renal pelvic carcinoma and another 2 patients developed carcinoma of the urinary bladder. All of them had been abusers of drugs containing phenacetin usually combined with phenazone and caffeine (phenacetin 0.5 g, phenazone 0.5 g, caffeine 0.1 g). No tumour developed in 88 non-abusers with chronic pyelonephritis followed up during the same period.

The manifest development of the tumour usually came some years after cessation of a heavy consumption of the drugs. The estimated mean consumption of phenacetin was 7.8 kg. Signs of nephropathy with renal papillary necrosis were found clinically, roentgenologically and/or histopathologically in all patients except 4. The tumours were all malignant and of transitional cell type; squamous areas were seen within some. The co-existing nephropathy contributed to the poor prognosis in this series in which the 5-year survival was 27%.

Clemmesen (Cancerregisteret, Copenhagen) reported that occupational cancer was not a problem in Denmark though some studies in Denmark and in New Orleans had shown an association with cigarette smoking and with carcinoma of the bronchus. He commented that there did not seem to be any parallelism between the national rates for bronchial carcinoma and bladder tumours. Other authors discussed the epidemiology of occupational cancer and, in addition to the well-established risks in the dye and rubber industries, an increased risk has been shown among tailors, nurses and hairdressers in the Leeds area by Anthony and Thomas (Department of Experimental Pathology and Cancer Research) whilst Cole, Hoover and Friedell (Harvard University, Boston) emphasised the increased risk in the leather industry. Occupational cancer in the Midlands was discussed by Veys (North Staffordshire Medical Institute), who pointed out that the mortality from cancer of the bladder has been rising slightly over the last 10 years and that there are local variations in the mortality. Using a notification scheme for all patients dying of bladder tumour in his area he obtained postmortem examinations of 105 male and 25 female cases. He considered that occupational factors might be realistically implicated in up to 20% of the male patients but the incidence was much lower in the females in whom special factors seemed to be operating.

Yoshida, Harada, Miyakawa and Kato (Kyoto University, Japan) pointed out that it was important to investigate occupational bladder cancer not only in the workers in the dye-stuff industries but also among users of the dyes, and they noted an increased incidence in workers in the traditional silk painting, who moisten the brush with the tongue. Owen (Department of Employment and Productivity, London) discussed the various methods of reducing occupational risks by surveillance including cytological examination of the urine every 6 months, and the restrictions on the manufacture and use of certain known carcinogens in the Carcinogenic Substances Regulations, 1967. These regulations also demand that each worker employed in connection with certain other controlled substances receive an approved cautionary card on termination of his employment. Torres (Laurencio Marques) reviewed the role of bilharzia in Africa and concluded that it was responsible for the marked increase in squamous carcinoma observed in that area, the number of transitional cell carcinomas being very small.

In summarising, Higginson indicated that considerable progress has been made in relation to studies on occupational hazards, and suggested that this group represented only 10% of all bladder cancers. The possibility that cigarette smoking was partly responsible for many of the remaining tumours clearly required consideration, as did the possible pollution of the general environment by industrial carcinogens escaping from various sources. He mentioned the report linking coffee drinking and bladder cancer (Cole, 1971) and drew attention to the fact that this had not yet been confirmed, and further that there was some discrepancy in the data between the sexes.

Immunology and Pathology

Bubenik, Perlmann, Helmstein and Moberger (Wenner-Gren Institute, Stockholm) investigated the immunological response in patients with bladder tumours, using a micro-assay in disposable tissue culture plates to demonstrate cellular and humoral immune responses to human urinary bladder carcinoma. Leucocytes isolated from peripheral blood of 17 out of 19 patients with bladder carcinomas were cytotoxic for autochthonous as well as for allogeneic bladder carcinoma cells *in vitro*. The cells from all of 11 individual bladder carcinomas studied were susceptible to this cytotoxic action of the patients' leucocytes. In contrast, no cytotoxicity was observed when cells from unrelated tumours or various normal tissues were used as target cells. Purified blood lymphocytes from patients whose leucocytes were active, were also cytotoxic. Sera of 8 out of 13 patients with bladder carcinomas contained complement-dependent antibodies which were cytotoxic for autochthonous and allogeneic bladder tumour cells. When serum was taken from the same patient on different occasions over a period of 8 months cytotoxicity was found in

some samples but not in others. Sera from 4 of 9 patients exhibited a blocking activity, which completely abolished the cytotoxic effects of patients' leucocytes. The serum of 1 patient contained antibodies which were not cytotoxic without leucocytes but which conferred a cytotoxic activity on to leucocytes from control subjects. This opsonising antibody was complement-dependent and of IgM nature.

The results indicate that the human urinary bladder tumours possess tumour-specific antigens which cross-react with each other.

O'Toole, Perlmann, Unsgaard and Edsmyr (Wenner-Gren Institute, Stockholm) described the effects of radiotherapy on the cellular response to carcinoma of the bladder. They used a microcytotoxicity assay to detect specific destruction of bladder tumour cells by purified peripheral blood lymphocytes. Serial tests were made on individual patients with carcinoma of the urinary bladder to monitor the cellular response to tumour in relation to the clinical situation. The incidence of lymphocyte cytotoxicity varied with the clinical staging of the disease. Thus 14/16 patients with stage T₁-T₂ tumour had cytotoxic lymphocytes before treatment, while the corresponding figures for stages T₃ and T₄ were 4/9 and 3/8 respectively.

Local radiotherapy in tumour doses varying from 3,500 to 8,400 r resulted in the disappearance or severe reduction of the cellular response in 10 cases studied. This suppression lasted as long as the irradiation given was continuous. At the cessation of radiotherapy all patients with stage T₁-T₂ tumours (5/5 studied) redeveloped cytotoxic lymphocytes. Of those with stage T₃ tumours 8/10 had cytotoxicity after therapy and for stage T₄ the figure was 4/8. Among the 6 negative cases in the latter groups, 4 developed fatal distant metastases and 2 had large residual infiltrating tumours; this was observed within 12 weeks after radiotherapy. While the patients with stage T₂ tumours always redeveloped cytotoxicity after treatment, in some of those with stage T₃ and T₄ tumours no response returned or a response was induced in patients showing no activity before treatment.

The responses appearing after radiotherapy have been maintained during an observation period of 1 year. In several patients the responses declined after 6 to 12 months and this was usually associated with the appearance of metastases or recurrence. The patients who maintained high levels of cytotoxicity remained clinically tumour free. In patients given radiotherapy from 18 months to 10 years before testing the presence of a cellular response was usually associated with the continued presence of tumour.

These results suggest that the cellular response which can develop after irradiation is not maintained over a long period (*i.e.* about 2 years). Lymphocyte cytotoxicity seems not to be maintained in the absence of viable tumour or tumour material released as a result of necrosis, as after local irradiation of tumour. However, other critical factors may be the quantity and localisation of these materials as exemplified by some of the stage T₃ and T₄ tumour patients before and after treatment.

Melamed (Memorial Hospital, New York) discussed urinary bladder papilloma with carcinoma-in-situ. Papillary tumours of the bladder contain an epithelial component that may be cytologically benign or malignant. By definition, the former are considered papillomas and the latter papillary carcinomas. Occasionally, otherwise benign papillomas will have limited areas of epithelium that are histologically and cytologically malignant, though non-invasive. This he calls carcinoma-in-situ within a papilloma. It has been demonstrated that carcinoma-in-situ within non-papillary epithelium is an early stage in the development of invasive carcinoma. By analogy he theorises that carcinoma *in situ* within a papilloma also represents an early stage in the development of invasive carcinoma.

Of approximately 800 patients with bladder tumours seen at Memorial Hospital from 1965 through 1970, 41 (5%) had carcinoma-in-situ within a papilloma. The age range was 41 to 83 years, with 1 individual aged 25; 27 were men and 14 women; 4 men had possible exposure to chemical carcinogens. There was a past history of bladder or renal pelvic papilloma or papillary carcinoma in 27 patients and infiltrating non-papillary carcinoma in 2 patients; 12 patients (29%) had no

prior tumours. Of the 12 patients presenting initially with carcinoma-in-situ within a papilloma, all were treated by transurethral resection—2 later developed invasive carcinoma, 4 had recurrent papillomas with carcinoma-in-situ, and 1 had a subsequent benign papilloma. Four patients remain free from recurrent tumour and 1 has been lost to follow-up.

Papillary carcinoma can be postulated to arise:

1. by proliferation of mucosa already showing carcinoma-in-situ;
2. by proliferation of normal mucosa simultaneous with the transformation from benign to malignant epithelium; or
3. by diffuse or focal malignant transformation of epithelium in a preformed benign papilloma.

The clinical association of papillary carcinoma with papilloma suggests that the third mechanism may be very common and the course of events in his patients is consistent with this view, which may be summarised as follows:

Normal bladder mucosa→Papilloma→Papilloma with carcinoma-in-situ→Papillary carcinoma and invasion.

Melamed also presented studies on cytology in the follow-up of patients after treatment of bladder cancer. He favours cytological investigation because of the known multifocal origin of carcinoma of the bladder, and the associated high probability of carcinoma arising elsewhere in the mucosa of the urinary tract. At least 8% of patients who have had cystectomy for carcinoma of the bladder can be shown to have carcinoma-in-situ of the ureter, and more than half the patients with renal pelvic tumours have had or will develop other urothelial tumours. Cytological examination of the urinary sediment provides a sensitive and accurate means of evaluating the urinary tract epithelium. Malignant cells are shed early and often abundantly from carcinomas and carcinoma-in-situ of the urothelium. By following the cytology before and after resection of a bladder carcinoma, it is possible to confirm the adequacy of resection or to indicate that tumour remains. By examining the urinary cytology at 3- to 6-month intervals thereafter, it is possible to detect any newly forming carcinomas at an early stage. Even when patients have had total cystectomy for bladder cancer with construction of an ileal conduit, he finds that later development of upper urinary tract carcinomas can be detected by cytology. If the urethra remains he recommends that cytological specimens should also be obtained by urethral irrigation at regular intervals.

Irradiation and the chelating drugs used in cancer chemotherapy can cause epithelial (and stromal) abnormalities that may make cytological diagnosis more difficult. In experienced hands, and with the knowledge of the clinical setting, these changes, and others due to surgery, can be recognised and properly identified. Cytology is a supplement to the other techniques used for following patients after treatment of bladder cancer. It may lessen the need for frequent cystoscopic examinations but does not substitute for cystoscopy, for the routine urinalysis nor for any of the other diagnostic procedures. It can be used effectively to detect early or occult carcinomas that might otherwise be overlooked and for that purpose has an important place among the investigations available to the urologist.

Anderson (Leeds) described the changes produced by high-energy radiation both in tumours and in the epithelium and wall of the bladder. The changes had been studied by conventional histological techniques, including whole circumferential bladder sections, during a 10-year period from 1961 to 1970. Material was obtained from endoscopic biopsy (215 cases), from primary cystectomy within 4 to 12 weeks following pre-operative radiotherapy (in 7 cases), from secondary cystectomy (33 cases) performed 9 months to 8 years after the completion of a radical course of radiotherapy and from postmortem (62 cases). In the secondary cystectomy group the indications for operation were residual or recurrent tumour, or bleeding or both.

The early changes seen in all groups, but especially in the primary cystectomy specimens,

were those of epithelial cell swelling, nuclear pyknosis, cellular mucoid change, mitotic abnormality and epithelial cell necrosis—in the epithelium of both the tumour and the bladder. The connective tissue showed oedema, vascular hyperaemia and inflammatory cell infiltration.

Later changes (persistent irradiation reaction) were best seen in secondary cystectomies and postmortem material. Again changes were observed in both epithelium and connective tissue. The epithelial changes included cellular and nuclear irregularity persisting up to 4 years after external irradiation with Cobalt-60 (in patients with no residual bladder tumour) while the connective tissue changes included muscular fibrosis, submucosal oedema and fibrosis and the formation of thick-walled blood vessels with vascular sinusoids. The prostate gland showed stromal fibrosis and epithelial atrophy.

These changes might cause severe clinical symptoms or go completely unnoticed. In a small proportion of the cases, surface healing of tumours occurred with islets of surviving tumour cells persisting deeper in the bladder wall.

Radiotherapy does not appear to diminish or enhance in any way the tendency to form tumours.

Clinical

Anderson, Clark, Smith and Williams (urologists, Leeds) reviewed 299 unselected new patients with bladder tumours treated between 1965 and 1967. Of these, 40% died within the first year and the overall 3-year survival figure was 42%. In the initial staging 29% of tumours were found to be mucosal, 26% muscular, 28% extra-vesical and 6% fixed to the pelvic wall. 61% of tumours were well differentiated, 40% poorly differentiated and 17% were anaplastic. Half the tumours showed evidence of invasion at initial assessment.

In this series tumours staged as T₁ and T₂ were treated by transurethral resection while stage T₃ and T₄ tumours were treated primarily by radiotherapy. Patients in whom transurethral resection failed and who subsequently developed invading tumours were then treated by radiotherapy, while cystectomy was reserved for patients in whom radiotherapy failed.

These survival figures were not corrected for death from intercurrent disease which, in the age group concerned, would account for approximately 15% of the deaths. They are similar to those reported by Miller, Mitchell and Brown (1969) and to those reported to the conference by Cifuentes Delatte (urologist, Madrid) whose overall 3-year survival in 1,034 treated patients was 55% and who also described a codified case record adapted for use by computer analysis.

Among those attending the conference there was general agreement on treatment of stage T₁ lesions by endoscopic means, but opinions on the treatment of stage T₂ and T₃ lesions varied, some preferring surgery and others radiotherapy. Some of the arguments put forward are summarised below.

Frank (radiotherapist, Leeds) reviewed 181 patients treated by radiotherapy during the years 1960 to 1963 inclusive. They were given either a radical (106 patients) or a palliative (75 patients) course of high-energy radiation. Excluding those dying of intercurrent disease, the overall 5-year survival was 33%. Of those patients given radical treatment, there was a marked fall in survival between stage T₂ (57%) and stage T₃ (31%). In all clinical stages the survival rate remained stationary from the end of the third year to the end of the 5-year follow-up period. This indicates that after 3 years there may be some relaxation of the rigid follow-up regime in those patients who have remained recurrence- and symptom-free for this length of time. Complications included telangiectasia (10%), contracted bladder (7%) and pelvic fibrosis (3%). These were usually asymptomatic and were fortuitous findings at follow-up examinations. However, 2 patients with telangiectasia required total cystectomy to control the bleeding. Other complications were rare. The author concludes that radiotherapy is the treatment of choice for those tumours in stages T₃ and T₄ and for those in stage T₂ which cannot be controlled by endoscopic means. The multiple papillary type of tumour—usually stage T₁—does not respond to radiotherapy and should be treated by total cystectomy if not controllable endoscopically.

Pointon (radiotherapist, Manchester) reviewed 329 cases of bladder carcinoma treated over 3 weeks by a radical course of megavoltage (4 MV) therapy; no case had received previous treatment. 22% of these patients had mucosal lesions, in 26% muscle was invaded and in 52% the lesion had extended beyond the bladder wall. Among the features considered were multiplicity of tumours, macroscopic type and histology. Stage-for-stage no statistically significant difference in results could be attributed to these factors. Complications included bowel problems (3%), contracted bladder (2.7%), and telangiectasia (2%). He considered the pyelographic findings in 313 of these patients and found evidence of obstruction or non-function of a kidney in 27% of stage T₂ (muscular) lesions and in 52% of stage T₃ (perivesical) lesions. Non-function of a kidney had an adverse effect on prognosis, but the presence of hydronephrosis or hydroureter was of less significance. He found no evidence of recovery in any non-functioning kidney following irradiation.

Edsmyr (radiotherapist, Karolinska Sjukhuset, Stockholm) compared 2 groups each of 300 patients with bladder tumours. The first was treated between 1952 and 1956 by surgery alone and the second between 1957 and 1964 using a supervoltage technique giving a mean tumour dose from 6,500 to 7,000 r over a period of 6 to 8 weeks. The 5-year survivals of lesions in stages T₂, T₃ and T₄ treated by irradiation were respectively 34%, 25% and 7%, while those for similar lesions treated surgically were 22%, 8% and 0%.

The 2 groups were not strictly comparable because of certain minor differences in stages, since stage T₃ in the surgical series included only those cases in which the tumour was histologically confined to muscle whilst stage T₃ in the irradiated series included tumours which were both palpable and mobile. He concluded that primary supervoltage therapy should be the method of choice in those patients in whom tumour had spread to the perivesical tissues.

He also noted that of the patients treated by radiotherapy who died within 5 years, only 10% were free of tumour within the bladder. Consequently he is now recommending that patients with stage T₂ lesions whose tumour is of high malignancy should receive pre-operative irradiation of 4,000 to 4,500 r over 5 to 6 weeks followed after an interval of 1 month by cystectomy. His present overall policy may, therefore, be summarised as follows:

Not palpable (T₁-T₂) malignant grade 1-2—surgery.

Not palpable (T₁-T₂) malignant grade 3-4—pre-operative irradiation followed by cystectomy.

Palpable (T₃) and immobile (T₄)—irradiation alone—the full course of treatment.

Van der Werf-Messing (radiotherapist, Rotterdam) observed 1,000 patients with proven carcinoma of the bladder since 1950. Of these, 636 patients underwent potentially curative treatment with either external irradiation (300) or radium implant (336). The 5-year survival in all groups was approximately twice as high in patients receiving implantation and being for stage T₁, T₂ and T₃ lesions approximately 85%, 70% and 22% respectively, compared with 50%, 35% and 12% in those treated only by external irradiation. Following tumour deposits in the scar in certain of the early cases the technique of radium implantation was modified in 1962 to include the use of 3 × 350 r to the true pelvis before operation. This resulted in a further minor improvement in stages T₁ and T₂ (5-year survival for stage T₁: 90%, stage T₂: 75%) and increased 5-year survival rate in the stage T₃ category to 45%. The latter improvement was due to complete prevention of scar-implants and to a significant reduction in haematogenous spread.

She also noted that of 88 patients considered unsuitable for radium implantation and treated by pre-operative irradiation followed by cystectomy, a T-stage reduction occurred in about 60% of the cases. This reduction was not related to the degree of differentiation of the tumour, and it was notable that nearly 30% of the tumours seemed to have disappeared on examination of the cystectomy specimen. Patients with such T-stage reduction had, as one might expect, a significantly better prognosis than those without (stage T₂: 60%, stage T₃: 80% 5-year survival).

Bloom (radiotherapist, London) reported 32 patients with bladder tumours invading deep muscle or perivesical tissue (stage T₃) treated by limited pre-operative pelvic irradiation (4,000 r

in 4 weeks) followed 4 weeks later by radical cysto-prostatectomy with clearance of pelvic nodes. In 28% of patients no tumour was found at cystectomy whilst there was a significant reduction in T-stage in a further 20% of patients.

Histologically positive nodes were found in 13% of patients against an expected incidence of some 50% reported in patients treated by surgery alone. After 3 years, 55% of this small group of patients are still alive, which suggests that this combined treatment may well have advantages over a radical course of irradiation alone, in which the survival in his experience has been only 20% after 3 years.

This programme of treatment required 12 weeks for completion. This time could, however, be reduced by a low dose and short-time pre-operative irradiation (e.g. 1,000 r over 2 days or 2,000 r in 5 days) followed by immediate surgery; this would have the advantage of reducing the overall time of treatment to 4 or 5 weeks. Radical radiotherapy following partial cystectomy appeared to be of particular value in cases of deeply infiltrating, undifferentiated tumours. In a retrospective study of 35 patients with stage P₃ solid, anaplastic carcinomas the 5-year survival was 26%, compared with only 8% of 38 patients of similar stage treated by partial cystectomy alone.

Whitmore (urologist, New York) reported upon his indications for and results from cystectomy in 327 patients with bladder tumours. He believes that cystectomy is indicated for low-stage tumours when these are multiple, are showing rapid or multiple recurrences and for high-grade

Table

Percentage of 5- year Survival following Total Cystectomy (Whitmore)

	T ₁ , T ₁ T ₂	T ₃	T ₄
Surgical series	43	20	...
Protocol series	52	34	25
Non-protocol series	34	23	...
Contemporary series	57	33	16
Protocol radiotherapy series only	53	15	25

lesions, and that cystectomy is indicated in high-stage cases in those patients in whom segmental resection is unsuitable because of multiple tumours, a history of prior tumour elsewhere in the bladder or the proximity of the tumour to the bladder neck. He uses a combined technique of pre-operative irradiation of 4,000 r in 4 weeks to the true pelvis followed by total cystectomy 4 to 6 weeks after the course of radiotherapy finishes. In assessing the results, he refers to this as the protocol series whilst patients treated by other techniques are referred to as non-protocol cases.

Approximately 70% of the patients explored underwent cystectomy in each group and the incidence of death after operation and of complications was similar in each group at approximately 12% and 43% respectively. Dr Whitmore added that 20% of patients had a reduction in stage following the pre-operative radiotherapy. Using the protocol treatment, the 5-year survival was no better in stages T₁, T₁, T₂ and T₃ but was notably better in stage T₄ than that of a previous group of patients treated without any form of radiotherapy. These results are recorded in the Table together with those of the contemporary regime in which the patient received 2,000 r in 8 days before cystectomy and that of the results of protocol radiotherapy only in which the patient either refused subsequent cystectomy or in which the surgeon subsequently declined to operate. In this last group the results of the treatment of low-stage lesions are at least as satisfactory as those of cystectomy, though patients with stage T₃ lesions fared less well.

Dr Whitmore also compared the clinical stage with the pathological stage at radical cystectomy

and found that the clinical staging was correct in 69% of stage T₁, T₁ and T₂ lesions, 45% of stage T₃ lesions and 62% of stage T₄ lesions.

Kerr (urologist, Toronto) reported that the 5-year survival of all patients with bladder tumours in Toronto is 39% and commented upon his results obtained using enterocystoplasty following cystectomy in 50 patients (46 males and 4 females). Total cystectomy was carried out on 44 patients, a simple cystectomy (*i.e.* not including a total prostatectomy) in 5 and partial cystectomy in 1. This was combined with ileocystoplasty in 28 patients, colcystoplasty in 17 patients and caecocystoplasty in 5 patients. Dr Kerr's view was that the ileum was the easiest of the 3 to use. He reported a 6% mortality, 75% 3-year survival and 60% 5-year survival.

28% of the patients had had some complication including a fistula at the urethral anastomosis in 7 patients, faecal fistula in 1, burst abdomen in 3, intestinal obstruction in 2, incisional hernia in 4 and other complications in 5 patients. One urethral recurrence was found in 28 patients followed up to 5 years. 23 of the patients were continent, 12 suffered from enuresis and 10 were incontinent including 2 women who underwent simple cystectomy (*i.e.* without urethrectomy) an operation which, in Dr Kerr's opinion, should not be carried out because of the combined possibility of urethral recurrence and incontinence.

Helmstein (surgeon, Soderjukhuset, Stockholm) reported a new method for the treatment of cancer of the urinary bladder by hydrostatic pressure with a water-filled balloon (Helmstein, 1972). This produced tumour necrosis by reduction of the blood circulating in the bladder wall. The procedure was carried out under high epidural anaesthesia and the increased intravesical pressure was maintained for 5 to 7 hours.

After hydrostatic pressure treatment total necrosis of tumour was found in 27 out of 35 patients and partial necrosis in 8 patients. Helmstein found that the highly malignant tumours were more sensitive to pressure than were those of lower malignancy and that to a large extent the results were determined by the duration of the increased pressure. He advised that, after technical failure of the treatment, the bladder should be rested for 1 week before repeating it and should muscle rupture occur, that at least 2 months should elapse before further treatment is given.

Williams and Jenkins (urologists, Leeds) reported 37 patients treated between the years 1961 and 1968 by radical cysto-prostatectomy and urinary diversion following failure of high-energy radiotherapy. In 24 of the patients severe persistent haematuria which failed to respond to conservative measures precipitated the need for the operation. All the survivors had been followed for at least 3 years after cystectomy.

While the operative mortality was high (25%), one-half of the survivors were still alive 3 years after the operation and 4 of the 10 patients available for follow-up analysis were alive at the end of 5 years. The staging of the tumours at cystectomy clearly influenced the outcome and the presence of tumour in the perivesical tissues or in the lymphatic vessels was associated with early death from metastatic carcinoma. Of the 14 patients alive after 3 years, 4 patients underwent subsequent urethrectomy for urethral tumour.

The authors suggest that one third of patients in whom radiotherapy fails may be salvaged by cystectomy and that when persistent haematuria is present cystectomy should be carried out without delay.

Summary

A bladder cancer conference sponsored by the U.I.C.C. and others was held in Leeds in September 1971, and considered both the clinical and scientific aspects of the disease. The more purely scientific contributions have been summarised elsewhere (*European Journal of Cancer* 1972). The papers of clinical interest emphasised the occupational hazards in the tailoring industry, in hairdressers, in nurses, in the leather industry and in certain Japanese silk painters. It seems likely that the overall incidence of bladder tumours is gradually increasing and that there is

likely to be an association with smoking. Emphasis was given to the importance of medical surveillance not only of workers in the dye industry but also of those using the finished products. The role of bilharzia in the production of bladder cancer was considered and it is believed that this is associated with an increase in squamous but not in transitional cell carcinomas.

The immunological consequences of radiotherapy were discussed and evidence was produced that high-energy radiation reduces the cellular response for the period of irradiation, though cytotoxic lymphocytes develop again soon after treatment ceases. If the cytotoxic response decreases again following radiotherapy it is usually associated with the appearance of metastases or local recurrence. Patients who maintain high levels of cytotoxicity remain clinically tumour-free.

The clinical papers emphasised the diverse nature of the treatments available. In terms of 5-year survival they highlighted again the fact that many forms of treatment can be used to control the superficial (stage T₁) tumours whilst, for the advanced (stage T₄) lesions, no treatment is effective. The 3- and 5-year survivals for stage T₂ and stage T₃ lesions are so similar, despite the different forms of treatment used, that it seems likely that it is impossible clinically to differentiate these 2 stages. Since the 5-year survival following the different forms of treatment is so similar it may be thought unlikely that any of the treatments used significantly modifies the natural course of the disease. There is certainly no strong evidence to suggest that primary cystectomy for stage T₃ lesions when compared with the results following a radical course of high-energy radiation, justifies the high immediate surgical mortality and long-term morbidity. On the other hand, if the results following pre-operative radiotherapy and cystectomy reported by Bloom are maintained in a larger series, the picture may well change.

In our opinion the results presented at the conference suggest that the best form of primary treatment yet available for invasive tumours of the bladder is external and/or interstitial radiotherapy, with the exception of those patients presenting with bilateral ureteric obstruction.

One notable feature of this conference was the lack of any contribution relating to the use of cytotoxic chemotherapy in the management of bladder tumours.

We should like to record our indebtedness to the U.I.C.C. and to the other sponsors, the International Agency for Research on Cancer, Yorkshire Cancer Research Campaign, Dunlop Limited, Imperial Chemical Industries Limited (Dyestuffs Division), John MacKintosh and Sons Limited, G. D. Searle and Company Limited, and several private donors without whose generous help it would not have been possible to hold this interesting and very informative meeting.

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A Trial of Polyglycolic Acid Sutures for Circumcision

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A synthetic absorbable suture material, polyglycolic acid (Dexon), was introduced in this country in 1969. Polyglycolic acid (PGA) is a homopolymer of glycolic acid, a simple α -hydroxy-acid, and is broken down in the body into carbon dioxide and water. Studies using ^{14}C labelling have shown that the highest tissue levels occur in the liver and gastro-intestinal tract and that excretion takes place mainly in the urine and expired air (Morgan, 1969). The possibility of toxicity is therefore remote and it has not been reported in man.

Favourable reports of the use of PGA in animals and in man have been made by a number of workers since its introduction. Its superior handling qualities and minimal inflammatory response have been repeatedly stressed. In rabbits, PGA sutures have been shown to retain greater tensile strength than chromic catgut after 7 days of implantation and have similar tensile strength to catgut after 14 days (Morgan, 1969; Herrmann, Kelly and Higgins, 1970). Absorption of PGA was complete by 60 days in these animals.

In view of these reports it was decided to compare PGA with catgut in a controlled trial in the operation of circumcision. This operation was chosen because direct observation is easy; the use of catgut for circumcision is often associated with marked tissue reaction, oedema and infection; the operation is commonly performed; and the remote, but just possible, teratogenic risk would be avoided. It was also hoped that the unsightly adhesions around the corona sometimes seen with catgut might not occur after using PGA sutures.

Materials and Methods

Patients admitted for circumcision were randomly allocated, according to whether their hospital number was odd or even, to 1 of the 2 main groups. In Group (1) the sutures used were catgut and in Group (2) the sutures used were of PGA (Dexon).

Group (1) patients were divided into 2 subgroups according to whether plain or chromic catgut sutures were used.

Table I
Age Distribution of Patients

Suture Material	Number	Age Range (years)	Mean Age (years)
Chromic catgut	14	2-45	8
Plain catgut	14	2-13	5
Polyglycolic acid	28	2-22	7

56 patients were accepted for the trial and the details are shown in Table I. All operations were performed by the author or by a supervised senior house officer, using the same technique.

Operative Technique

The prepuce was freed by blunt dissection and the glans exposed by a dorsal slit. Circumcision was completed and a standard frenular suture inserted. Meticulous haemostasis was obtained using 00 gauge ligatures of the appropriate suture material, and apposition of skin achieved by interrupted 00 sutures of the same material. Paraffin gauze was wrapped around the shaft and glans of the penis and a loose dry dressing placed over this. Stilboestrol 5 mg t.d.s. was given orally to patients aged over 16 the day before operation and continued for 1 week.

All follow-up examinations were carried out by an independent observer, who was unaware of the type of suture material used. Examinations were made on the evening of the operation, at the 3rd and 7th day, and thereafter at weekly intervals until the patient was discharged from follow-up. In each case a record was made of the degree of discomfort, local tissue reaction, and the number of sutures *in situ*.

Results

Patients were divided into those assessed as a "good" or "poor" result according to the severity of local tissue reaction or discomfort at 7 days. The results are shown in Table II.

Table II

Operative Results 7 Days after Operation

Suture Material	"Good" Result	"Poor" Result	Total
Chromic catgut	6 (43%)	8 (57%)	14
Plain catgut	5 (36%)	9 (64%)	14
All catgut	11 (39%)	17 (61%)	28
Polyglycolic acid	23 (82%)	5 (18%)	28

Table III

Persistence of Suture Material after Operation

Suture Material	Days <i>in situ</i> after surgery				
	14	21	28	35	42
Chromic catgut	10 (71%)	3 (21%)	..	..	..
Plain catgut	1 (7%)	...	...	..	..
All catgut	11 (38%)	3 (11%)	...	..	...
Polyglycolic acid	20 (71%)	15 (54%)	7 (25%)	4 (14%)	2 (7%)

It can be seen, from Table II, that 23 (82%) of the cases in which PGA sutures were used were assessed as "good" while only 11 (39%) of the cases in which catgut was used could be rated "good". This difference is significant ($\chi^2 = 9.06$, $P < 0.01$). The superiority of PGA at 7 days is most marked when the comparison is made with plain catgut where only 5 (36%) out of 14 cases were adjudged "good". This difference is again significant at the 1% level ($\chi^2 = 7.11$, $P < 0.01$). With chromic catgut the difference from PGA at 7 days when 6 (43%) of the 14 cases were rated "good" does not quite reach significance ($\chi^2 = 5.04$, $0.02 < P < 0.05$).

Table III shows the persistence of the various types of suture after operation. Catgut sutures were still present after 3 weeks in only 3 patients (11%) and in no case did they persist after 4

weeks. In contrast, PGA sutures were still present in 15 (54%) patients after 3 weeks, and in 7 (25%) patients after 4 weeks. Even at 6 weeks some PGA sutures were present in 2 patients and required removal at that time. The incidence of PGA sutures persisting at 6 weeks might have been higher since sutures were removed between 3 and 6 weeks after surgery in 9 other cases because of local discomfort.

Discussion

The ideal suture material varies with the requirements of individual operations (Ulin, 1971) and also to some extent with the requirements of individual surgeons. The synthetic polyglycolic acid absorbable suture has previously been compared with the only other absorbable suture in common use, catgut, and has been shown to have many advantages (Morgan 1969; Anscombe, Hira and Hunt, 1970). PGA may be preferable for subcuticular skin closure (Morgan, 1969) or for use in paediatric, vascular and intestinal anastomoses (Dardik, Dardik, Katz, Smith, Schwibner and Laufman, 1970), but the claim that it may be an ideal universal suture material (Dardik, Dardik and Laufman, 1971), or that it is superior to catgut in every instance (Anscombe *et al.*, 1970) may prove to be too broad a generalisation. Lichtenstein (1970) has already warned that the 40% loss of tensile strength of PGA sutures after 7 days, although an improvement on the 60% lost by chromic catgut after the same time, is of some concern, and suggested that they should not be used for closing supportive structures such as the aponeurosis of the abdominal wall.

In the present study it is seen that for circumcision the main disadvantage of PGA sutures is their tendency to persist after surgery causing mechanical irritation and discomfort. Sutures may still be present 4 weeks after circumcision and this would be considered unacceptable by many surgeons. The need to remove such sutures postoperatively is clearly a disadvantage and in the author's opinion PGA sutures are not recommended for circumcision. Nevertheless, this trial has demonstrated that the use of PGA sutures in this situation significantly reduced postoperative discomfort and local tissue reaction when compared with catgut.

Summary

A controlled trial is described in which PGA is compared with catgut as a suture material for circumcision. Of a total of 56 operations, PGA was used in 28, plain catgut in 14 and chromic catgut in 14. A good result, indicated by the absence of discomfort or local reaction after 7 days, was obtained in 82% of cases with PGA, in 43% with chromic catgut and in 36% with plain catgut sutures.

However, the finding that 25% of PGA sutures are still present at 28 days is a major disadvantage and their use can not be recommended in this particular operation.

I am very grateful to Mr Davidson, Mr May and Mr Bourns for permission and encouragement to perform this trial on patients in their care, to Mr Harding and Mr Dunley who did many of the operations, and to Dr Anderson, Dr Appleton and Dr Bishop for their postoperative assessments.

I would also like to thank Professor J. Peacock, Professor Sir James Fraser and Mr B. J. Wilken for their kind suggestions and comments.

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Comparison of Two Commercially Available Dipinocula with Standard Bacteriological Assessment of Bacteriuria

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Dipinocula techniques were originally introduced to overcome difficulties of measurement arising from the proliferation of organisms that occurs in urine between collection and bacteriological assessment in the laboratory. The dip slide was a logical extension of the method devised by Mackey and Sandys (1965, 1966) who used a spoon filled with solid culture medium as a form of dipinoculum transport medium.

Guttmann and Naylor (1967) showed that a glass microscope slide, coated with nutrient agar on one side and with MacConkey's medium on the other, was an efficient aid to quantitative urine culture in a urinary infection clinic. Arneil *et al.* (1970) showed the Uricult dipinoculum to be reliable at room temperature and on incubation, confirming the earlier results of Cohen and Kass (1967), who used comparable methods.

The present study was undertaken to compare the efficacy of 2 commercially available dipinocula (Oxoid and Uricult) with one another and with the standard technique of bacteriological assessment.

Patients and Methods

Since 1960 the Pyelonephritis Unit at the City Hospital, Edinburgh, has been recording the natural history of patients with chronic pyelonephritis, and evaluating different forms of therapy in the management of recurrent urinary tract infection (Murdoch *et al.*, 1966; Murdoch *et al.*, 1968). During 1971 the urine from 192 female patients attending this out-patient clinic was selected for intensive bacteriological study. The patients' ages ranged from 5 to 72 years (Fig. 1); 86 of them (40 per cent) were receiving long-term antibacterial therapy at the time of the study (Table I).

The mid-stream specimen of urine (MSU) was collected by the patient, without previous vulval cleansing (Turner, 1961; Murdoch *et al.*, 1966), after instruction by the clinic Sister (L. M.).

The dipinocula used were the Oxoid dip slide kit (Oxoid Ltd., London), and Uricult (Orion Pharmaceutical and Chemical Laboratories Ltd., Helsinki, Finland). The dipinocula were immersed in turn, immediately after collection of the MSU, by one of us (L. M.). The MSU and the 2 dipinocula were then sent to the laboratory together, the MSU having been refrigerated for a short period in the out-patient clinic. The time between voiding and the start of bacteriological testing was never more than 3 hours, during which period the MSU was refrigerated. All bacteriological examinations were undertaken by one of us (E. T. W.).

In the laboratory the inoculated dip slides were incubated at 37°C for 18 hours. The results were then interpreted according to the manufacturers' instructions, and were compared with those obtained by the routine laboratory technique for the detection of bacteriuria. This involves the culture of urine specimens on MacConkey agar, using a standard loop technique.

Standard Technique

A platinum loop of 3 mm internal diameter (SWG 26) is dipped vertically into a well-mixed mid-stream specimen of urine, and inoculated over quarter of a MacConkey plate, which is then incubated at 37°C for 18 hours. The weight of growth is then assessed, 200 or more colonies indicating a significant growth (10^5 or more organisms per ml of urine). Growths of 90-200 are regarded as equivocal, the specimen then being checked by carrying out a viable count. Less than 90 colonies is regarded as an insignificant growth.

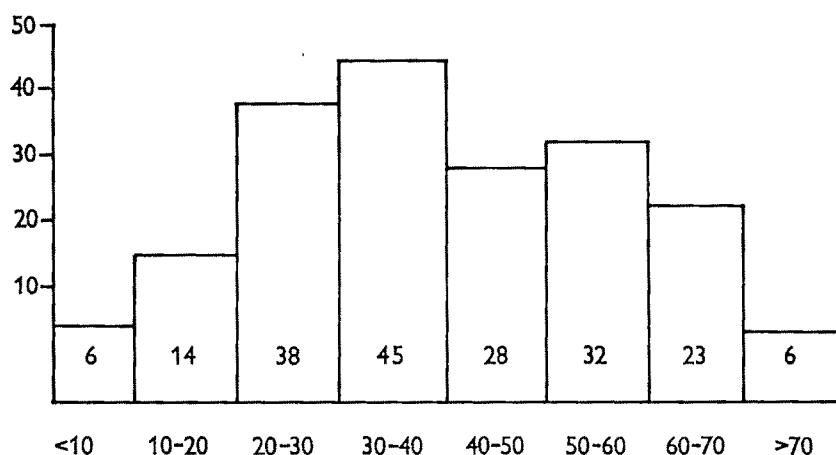


Fig. 1. Histogram showing age spread of the 192 patients.

Table I

Patients	Total No	No. on Long-term Treatment	% on Long-term Treatment	Cyclo-serine	Ampi-cillin	Corti-moxazole	Cepi-naletin	Nitro-lurantoïn	Nalidixic Acid
Bacteriuric	22	9	40.9	5	2	—	2	—	—
Abacteriuric	170	68	40.0	44	13	6	—	3	2
Total	192	77	40.2	49	15	6	2	3	2

A Gram film from the centrifuged deposit of approximately 10 ml of well-mixed urine is also examined to assess whether the specimen under scrutiny is a true mid-stream urine. More than a few epithelial cells and/or mixed flora of the type found in urethra, vagina or bowel, is taken to indicate faulty specimen collection. In these cases, an associated "significant" culture is regarded as being a contaminated one.

Results

At the time of the study 113 of the 192 patients were symptomatic, and 79 asymptomatic. The patients in the symptomatic group complained of dysuria, urinary frequency, or strangury, alone or in combination.

The total number of positive cultures by the standard method of testing was 22, an overall positivity rate of 11.4 per cent. Of this group, 17 were from the 113 symptomatic patients, making

a positivity rate of 15 per cent, and 5 were from the 79 asymptomatic patients, a positivity rate of 6.3 per cent.

Of the 22 patients with significant bacteriuria, 13 were not receiving antibiotic therapy, 5 were taking long-term cycloserine, 2 were taking ampicillin, and 2 cephalixin. The ages in this group ranged from 12 to 72 years, most being over 55 years (Fig. 2). The organisms isolated were *E. coli* (16), *Klebsiella* (3), and one each of *Proteus* species, *Enterococci*, and *Monilia*.

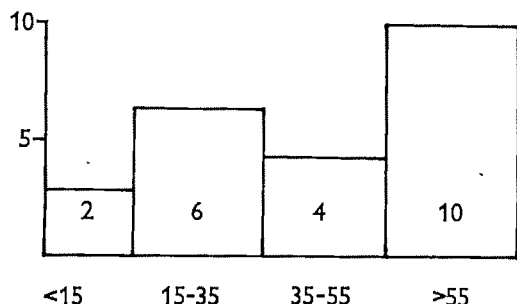


Fig. 2. Histogram showing the ages of 22 patients with positive cultures.

Comparison of Results with Oxoid and Uricult Dipinocula

In 20 of the 22 positive cases there was complete agreement between the results obtained from the dipinocula and those obtained by standard bacteriological assessment.

In 1 case the Oxoid dipinoculum and the standard testing showed a confluent growth of *Enterococci* but the Uricult showed no growth on either medium. It was not possible for the bacteriologist to tell whether or not this dipinoculum had been immersed in the urine sample under scrutiny. In 1 further case the MSU revealed a growth of *Monilia* on standard testing, which was not shown on either of the dipinocula. This represents a failure of the Uricult to detect 9 per cent and the Oxoid 4.5 per cent of the positives in this study.

In 6 patients in whom standard testing showed contamination of the specimen, the Oxoid showed a significant growth in 4 and the Uricult a significant growth in 5.

The incidence of confluent growth on the slides from urine with significant bacterial counts was 10 out of 20 Uricult, and 10 out of 21 Oxoid. By naked-eye examination it was impossible to decide whether or not the cultures were pure.

In 163 specimens (84.3 per cent) there was complete agreement (no significant growth) by standard testing and both dipinocula.

Discussion

This study has confirmed the reliability of the Oxoid and Uricult dipinocula for the detection of bacteriuria amongst women attending a hospital out-patient clinic.

The number of false negative results using the dipinocula was Oxoid 4.5 per cent and Uricult 9 per cent. These high figures reflect the comparatively small number of bacteriuric specimens in the study.

The number of false positives given by the dipinocula was Oxoid 2.1 per cent and Uricult 2.6 per cent, a probable reflection of contamination from faulty collection, despite prior instruction of the patients. Were this technique to be used by the patient herself at home, however, an even greater proportion of contaminated specimens might be expected. The relatively low contamination rate in this study may have been due to the instructions given by the clinic Sister, who also inoculated each dip slide.

The large proportion of positive urine cultures obtained is due to the highly selected group investigated.

To avoid unnecessary antibacterial treatment of patients whose dipinocula show equivocal or apparently positive results, a further MSU should be submitted for fuller testing in a bacteriological laboratory.

If these dipinocula had been used as the sole criteria of diagnosis of bacteriuria, then 2.1 to 2.6 per cent of the patients in this study would have received unnecessary antibacterial therapy.

Conclusions

Dipinocula techniques should be regarded as merely a screening procedure in areas where precise bacteriological assessment is available.

The dipinoculum technique is well suited to the screening of large numbers of women for bacteriuria in community surveys, while the reliability of dipinocula techniques at room temperature (Arneil *et al.*, 1970) makes this technique especially suitable for use in rural general practice where incubation is impossible and the laboratory remote.

Summary

Urine specimens obtained from 192 female out-patients attending a pyelonephritis unit were used to compare and contrast 2 varieties of commercially available dipinocula with one another, and with standard methods of bacteriological assessment.

The dipinocula produced reliable results comparing favourably with one another and with standard methods. The rate of false negatives was 4.5 per cent (Oxoid) and 9 per cent (Uricult), while that of false positives was 2.1 per cent (Oxoid) and 2.6 per cent (Uricult).

It is suggested that all patients in whom dipinoculum techniques indicate a positive, or equivocally positive, result ought to submit a further mid-stream specimen of urine for more critical bacteriological examination.

We gratefully acknowledge the generous supply of dipinocula from Oxoid Ltd., London, and Orion Pharmaceutical and Chemical Laboratories Ltd., Helsinki.

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Short Case Reports

Peripartum Hepatic Dysfunction and Xanthogranulomatous Pyelonephritis

A case of xanthogranulomatous pyelonephritis presenting as anaemia of pregnancy and puerperal pyrexia associated with persistent hepatic dysfunction is described.

Case Report. A 29-year-old female with no previous history of urinary disease presented with anaemia of pregnancy, post-partum pyrexia and jaundice. Examination revealed hepatomegaly and a hard mass in the left loin. Investigations showed a non-functioning left kidney with a pelvic calculus and urine cultures grew *E. Coli* and *Klebsiella*. Left nephrectomy was performed. The kidney which measured 16×10×8 cm showed the

pathological appearances of xanthogranulomatous pyelonephritis.

Postoperatively she became asymptomatic, but a year later there was still evidence of hepatic dysfunction with raised serum enzyme levels (5-nucleotidase 26 m.i.u./ml, adenosine diaminase 36 m.i.u./ml, guanase 3.8 m.i.u./ml and glutamate dehydrogenase 10 m.i.u./ml) and a persistently raised IgG.

Comments

The persistently abnormal liver function tests in this case, unlike the cases described by Vermillion

Table

Comparison of Pre- and Postoperative Investigations

Investigation		Normal Range	Pre-operative	Post-operative			
				9 days	6 weeks	5 months	1 year
Haemoglobin g/100 ml		11.5-16.4	7.7	11.0	11.2	13.3	13.6
E.S.R., mm/hr		0-7	160	131	78	25	28
Bilirubin mg/100 ml		0.2-1.2	1.5	1.1	...	...	1.0
Serum alkaline phosphatase King units		4-14	72.6	48	28	16.5	18.7
Immunoglobulins mg/100 ml of serum	IgG	500-1,600	2,060	...	..	...	1,720
	IgA	125-425	276	...	..	...	310
	IgM	47-170	116	...	...	...	146
Plasma proteins g/100 ml.	Total	6.0-7.2	6.7	...	7.4	7.2	7.4
	Albumin	3.7-5.1	2.7	...	3.5	4.3	4.0
	Globulin	1.5-3.5	4.0	...	3.8	2.9	3.4
5-Nucleotidase m.i.u./ml		5-11.5	17.2	...	18.7	9.8	26
S.G.P.T. m.i.u./ml		0-30	31	20	40	29	48
S.G.O.T. m.i.u./ml		0-30	9	17	58	35	35

et al. (1970) in which there was reversion of liver function tests to normal, suggests continuing hepatic damage while the isolated IgG increase is suggestive of an autoimmune phenomenon (Hobbs, 1970). Therefore although the immediate prognosis is excellent (Malek *et al.*, 1972) the long-term results may be poor due to continuing hepatic dysfunction.

We are indebted to Mr C. D. P. Jones and Dr K. H. Hardy for permission to report this case.

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Avulsion of a Long Segment of Ureter with Dormia Basket

A 50-year-old woman suffered right renal colic for 24 hours. I.V.P. showed a calculus measuring 5×7 mm situated 2.5 cm below the pelvic brim with delayed renal function and hydronephrosis on that side. She had fever which responded in 3 days to tetracycline. Nine days after admission a Dormia extractor was passed using an image intensifier. The stone was engaged at once but, as it approached the bladder, there was increasing resistance to withdrawal. When removed from the bladder the stone was firmly engaged in the basket and was followed by a long tubular structure, obviously the ureter. It seems likely that the ureter was ruptured at the site of the impaction and shortened concertina fashion, and that this bulk of tissue caused the increasing resistance felt as the extractor was drawn through the bladder wall before actual intussusception. The ureter was drawn taut, divided flush with the urethral meatus, and allowed to retract. Immediate I.V.P. showed extravasation at the level of the 4th lumbar vertebra. Right nephrectomy was performed. Convalescence was uneventful. A similar case has been reported by Hart (1967).

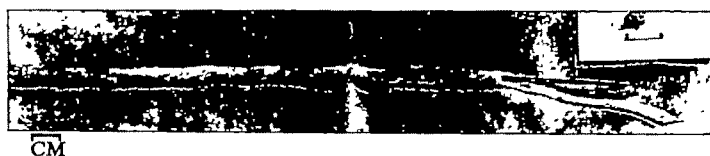
I am grateful to Mr R. W. Heslop, of Hull, for permission to submit this report.

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- HART, J. B. (1967). Avulsion of the distal ureter with Dormia basket. *Journal of Urology*, **97**, 62-63.

The photograph shows the avulsed segment, over a blunt probe, and the oxalate calculus. The length of ureter is partly an artefact due to stretching during the process of avulsion.



Congenital Megalo-urethra

A male child was admitted one day after birth with gross abdominal distension but able to pass urine. There was no anus and the penis was grossly enlarged. A colostomy was performed. The blood urea was 55 mg/100 ml and the haemoglobin 11.5 gm/100 ml. Seven days after birth an I.V.P. was done using 20 ml of Conray 420. It showed no function by the left kidney and poor function by the right. The child became dyspnoeic and cyanosed and died 3 hours later. At autopsy the striking abnormality was the penis. It was 10 cm long and covered, except near its root, with wrinkled skin of scrotal type. The prepuce was short and the external urinary meatus pinpoint in size. There was a rudimentary empty scrotum. The corpora cavernosa could be felt as flat bands on the dorsum of the penis. The penile urethra was hugely dilated but the membranous urethra was markedly stenotic. The prostate and the prostatic urethra were normal. The bladder was contracted and thick-walled. There was a diverticulum near to but separate from the right ureteric orifice. Both kidneys were hydronephrotic. The left ureter was very much dilated and tortuous. It ended blindly in the bladder wall. The right ureter was less dilated and opened into the bladder but through a markedly stenotic orifice. Both testes were situated above the internal rings. The left seminal vesicle, ejaculatory duct and adjacent vas deferens were absent. The rectum ended blindly in the region of the prostate and did not communicate with the urinary tract.

It has been postulated that megalourethra results from abnormal development of the corpus spongiosum and that its coexistence with other urinary tract abnormalities such as megacystis, megaureter, vesical diverticula or hypoplasia of the kidneys, suggest that the defect in the penile urethra is a manifestation of a more diffuse mesodermal abnormality.

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Fig. 1. Photograph during life.

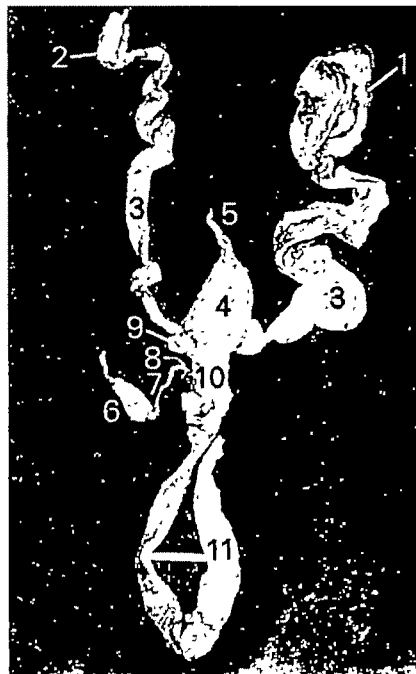


Fig. 2. Urogenital system after postmortem dissection, showing (1) Left kidney, (2) Right kidney, (3) Ureters, (4) Urinary bladder, (5) Urachus, (6) Right testis, (7) Vas deferens, (8) Seminal vesicle, (9) Diverticulum of bladder, (10) Megalourethra: a matchstick has been inserted into the urethra to show the dilatation. Note that the left testis has not been included in the specimen.

Book Reviews

Congenital Deformities of The Testis and Epididymis. By C. G. SCORER and G. H. FARRINGTON. Pp. x+203 with 94 figures. London: Butterworth and Co. 1971. £4.20.

The authors have managed to summarise their extensive knowledge of testicular descent into a useful monograph. Their clinical observations are carefully documented with objective evidence and explained with the liberal use of clear diagrams. All aspects of testicular descent are covered and the chapter devoted to the histological changes associated with mal-descent is of particular interest. Additional chapters cover torsion of the testis, inguinal hernia and hydrocele of infants.

This is a useful addition to a medical library but its cost will preclude a large private ownership.

J. P.

Vesicoureteral Reflux and Pyelonephritis. By JOHN A. HUTCH and ARJAN D. AMAR. Pp. 236. New York: Appleton-Century-Crofts. 1972. £6.30.

This new volume arriving so soon after the tragic death of John Hutch serves to remind us how much he has contributed to basic knowledge in urology. It was his initiative that first drew the attention of urologists to the problem of reflux, and his was the first standard operation for its correction. Since then he has contributed not only to the anatomy and physiology of reflux but also the study of bladder function as well as by his well known articles on the "base plate". This book is a review and retrospect of the past 20 years' work, and much of it will be familiar to urological readers, but it is valuable to have all this material clearly set out and well illustrated both diagrammatically and radiologically.

Both Dr Hutch and Dr Amar have been well known for their advocacy of early surgery in reflux cases and not surprisingly, therefore, this volume has a distinctly surgical bias; it will appeal more to urologists than to physicians or paediatricians in spite of the importance of the topic to medical management. It is surprising in view of Hutch's work on the maturation of the intramural ureter that the natural history of the condition and the chances of spontaneous recession receive relatively little attention. The style is informal, occasionally opinionated, and it is not always clear whether the opinion given is adequately backed by statistics or not. This is certainly a book which all trainees in urology should read, and one that should be available for reference in all urological libraries.

D. I. W.

Ureteral Dynamics. By S. BOYARSKY and P. C. LABAY. Pp. ix+493, 338 figs., 173 tables. Baltimore: Williams & Wilkins. 1972. (Edinburgh: Churchill Livingstone.) £7.00.

The contents of this book represent a compilation of the results of 9 years' research into the dynamics of the ureter. There are sections on the physiology, pharmacology and neurohistochemistry of the ureter, and *in vitro* and *in vivo* methods of studying ureteric function are described. In the final chapter, the applications of this research to the pathophysiology of disease of the ureter are considered.

This work is presented as part of the recent "information explosion" that has accompanied medical research in the USA. Each chapter is packed with numerous experimental results, and more results are included on microfilm inside the back cover. Unfortunately this wealth of experimental data makes critical assessment of the significance of the results extremely difficult, and a succinct summary of the main conclusions would have been most welcome. Nevertheless, this book will provide a mine of information for those interested in the experimental aspects of ureteral dynamics, provided that they have the time and the patience to sift through all the information presented.

W. F. H.

Genetics and the Urologist. By JOHN K. ORMOND, DALE R. DREW and KENNETH L. ÜRWILLER. Pp. 98 with 20 illustrations. Springfield: Charles C. Thomas. 1972. £4.04. (\$9.50).

Contained in this book is a readable and up to date, if somewhat superficial account of genetics in general and some thoughtful but rather portentous comments on the social and humanitarian problems posed by hereditary and congenital disorders. However, in view of its title and authorship it is disappointing to find that the book

includes only one short chapter on the hereditary aspects of renal and urinary tract disorders which, in parts, is so vague and sketchy as to be almost meaningless. Perhaps it succeeds in fulfilling the aim of the authors who set out to provide a general review of genetics for those whose knowledge of the subject has become "more or less rusty". It cannot, however, be recommended to any physician or surgeon who has a really serious interest in genetically determined disorders of the urinary system.

A. R. H.

High-dose Urography in Oliguric and Anuric Patients. By PAUL F. G. M. VAN WAES. Pp. 165 with 47 illustrations. Amsterdam: Excerpta Medica. 1972 £6.91 (US\$16.25).

The technique of drip infusion pyelography was first described in 1964, since when there has been considerable research into the pharmacology of urographic contrast media and their practical application, particularly in renal failure. In the first part of this monograph the author provides a valuable review of this literature. In the second part he gives the results of his own observations and experiments. For example, he shows that haemodialysis removes from the extracellular fluid all the contrast media in current use at a rate which is almost equal to that of normally functioning kidneys; also that extrarenal excretion, although recognised most frequently in renal failure, always occurs, and, if delayed films are taken, may be seen on the radiographs of people with normal renal function. The last part of the book is taken up with lengthy case reports illustrated by radiographs which sometimes, presumably due to poor reproduction, fail to show the features referred to in the text. This is disappointing when they are meant to show new observations, such as opacification of the rectal mucosa.

It is unlikely that everyone would agree with the author's conclusions that selective arteriography is the investigation of choice for assessing the renal parenchyma and that the need for retrograde pyelography can be almost completely eliminated by the use of high dose excretion urography. In addition, he makes no reference to antegrade pyelography which can be useful when oliguria is due to obstruction.

The presentation is excellent with helpful headings and a margin for annotations which could prove useful in a subject which is developing as rapidly as this. The book is recommended for anyone wishing to catch up with more recent developments in excretion urography.

W. S.

Scientific Basis of Surgery. 2nd Edition. Edited by W. T. IRVINE. Pp. xi+677, with illustrations. Edinburgh: Churchill Livingstone. 1972. £9.50.

Designed to help the surgeon keep up with scientific progress in his own and allied fields. The aim of this book is to derive principles of management from an understanding of primary function at tissue and organ level: in several sections, this is admirably achieved. Water and electrolyte metabolism, and the adrenal cortex are well described by Professor Victor Wynn, and pheochromocytoma is considered in detail by J. J. Brown. The parathyroid glands and calcitonin are fully discussed by D. H. Clark and B. E. C. Nordin. The sections on wound healing, shock, infection in surgical patients, deep vein thrombosis, and cancer immunology will prove of general interest.

The sections on pure urology are written by R. J. Luck. The basic physiology of renal function is well described, and the aetiology of acute renal failure is outlined, but the principles of management of acute and chronic renal failure could profitably have been considered in more detail. The dynamics of the renal pelvis, ureter and bladder are described, but pyelonephritis, urinary infection and neoplasia receive scant attention. Benign and malignant disease of the prostate are described, but there is little new information; the testicle is not considered at all. Renal transplantation is described as part of a review by Professor R. Y. Calne.

This second edition has been considerably revised, and many of the references have been brought up to date. The urologist may find this a useful reference book, particularly on the more general aspects of surgical practice.

W. F. H.

Progress in Biochemical Pharmacology. Series Editor: *Paoletti, R.* (Milan). Vol. 7: **Drugs Affecting Kidney Function and Metabolism.** Volume Editor: *Edwards, K. D. G.* (Sydney). Pp. xiv+536, 73 figs., 20 tables. 1972. Basel: Karger. SF190. -/DM 170. -/US \$53.20/£20.90.

The editors have presented in this book a number of outstanding reviews, by authors of international repute, covering the major areas of drug therapy in relation to renal disorders. The book is highly readable and clearly written, and contains a useful and generally well-selected bibliography. The division of chapters into shorter sub-sections makes for easy reference to special subjects of interest. The subject matter includes shock and renal haemo-

dynamics, diuretics, renal and adrenal hormones, acid-base regulation, effects of toxic agents on the kidneys, analgesic nephropathy, hypertension, acute and chronic renal failure, diet and dialysis, and drug therapy in renal transplantation. There is also an excellent section on antibacterial therapy for urinary infections. Always the emphasis is on the clinically important aspects of renal physiology and clinical pharmacology.

Though primarily of interest to the physician and nephrologist the book will serve as an excellent reference work for urologists. The high price may unfortunately discourage the private buyer but all urological departments should make sure the book is available for consultation in an easily accessible library.

P. R. U.

Clinical Organ Transplantation. Edited by R. Y. CALNE. Pp. 539+xi, with illustrations. Oxford and Edinburgh: Blackwell. 1971. £8.00.

Provided by this book is a comprehensive review of all aspects of organ transplantation, with sections from many specialist contributors effectively united under the general editorship of Professor Calne.

The first part provides the theoretical background to transplantation and contains sections on the allograft reaction, immunosuppression and organ preservation. The sections on tissue typing are comprehensive, and the case for effective collaboration between centres in order to provide an adequate recipient pool is well stated.

The second part is devoted to clinical kidney transplantation, with sections on live and cadaveric donor selection, kidney removal, and preservation techniques. Pre- and postoperative management, anaesthesia and operative techniques are described, and the sections on immunosuppression, management of complications, follow-up and long-term care are good. The pathology of renal transplants is particularly well described and illustrated. The succeeding parts are devoted to transplantation of other organs, and the problems that these procedures entail are accurately recounted.

There is no doubt that this will become the standard textbook of clinical transplantation, and it is to be hoped that it will reach a wide medical readership. The final chapter by Professor Calne, on Ethics, the Law and the Future of Transplantation, should become recommended reading for all medical students, if the techniques described in this book are to be developed sufficiently to allow more than the present 10% of young people with terminal renal disease to be treated by dialysis and transplantation, out of more than 2,000 dying each year in the United Kingdom.

W. F. H.

Radiology in Renal Disease. Ed. T. SHERWOOD. *British Medical Bulletin*, Vol. 28, No. 3. London: The British Council. 1972. £2.25.

This edition of the *British Medical Bulletin* contains a variety of papers which will be of value to anyone interested in diseases of the kidney. 15 topics are presented, including the use of ultrasound and isotopes in addition to conventional diagnostic radiological procedures. Some are reviews of the present body of knowledge. Subjects such as the renal toxicity of contrast media and the patterns of bone disease in renal failure are dealt with in this way. Others deal with the authors' personal research into subjects such as medullary necrosis in infancy and post-obstructive renal atrophy. The technique and uses of needle nephrostomy are well described as are methods of demonstrating changes in the small renal arteries in both experimental animals and man.

The standard of publication is excellent and the radiographs are particularly well reproduced on separate glossy pages. The editors have achieved their aim of presenting some of the important advances in the field of radiological research related to renal disease. However anyone reading this hoping to catch up with present day thinking in urinary tract radiology may be a little disappointed at some of the articles, which either present information already available in other texts or deal at excessive length with results of research projects. In this way the journal tends to fall between two stools, but apart from this it is highly recommended.

W. S.

Problems in Paediatric Urology. Edited by J. H. JOHNSTON and R. J. SCHOLTMEIJER. First edition. Pp. 301, with 170 illustrations. Amsterdam: Excerpta Medica. 1972. Price in England (August 1972): £11.44.

This is an interesting, stimulating and also in parts even an entertaining book to read. As the Editors state in their introduction, no attempt is made to cover the entire field of paediatric urology. Amongst the contributors are

urologists, paediatric surgeons and paediatric urologists. Inevitably, some of the subjects selected overlap from one chapter to another and it is entertaining to read diverse views expressed within the same book. The Editors must be congratulated on their restraint from attempting to co-ordinate the views of their contributors.

The problem of the decompensated ureter is very well reviewed. The anatomical improvements that can be achieved by "tailoring" and reconstructing the ureter throughout its whole length appear radiologically dramatic. Hendron also claims considerable improvement in function as estimated by pressure recordings taken within the lumen of the ureter.

In the chapter on ectopic ureters and ureteroceles, there are some attractive diagrams which are most helpful in an attempt to clarify the embryology. This section is so lucid and interesting that it merits a longer proportion of the book. It is disappointing to see no reference or acknowledgment to the earlier work of Nils Ericsson.

It is said that every urologist sometime in his life makes an attempt to reconstruct an ectopia vesicae and, at best, the result is a healthy bladder with a very limited urinary control. Mr Innes Williams describes his experiences and success with exstrophy of the bladder and considers that if there is an adequate amount of healthy mucosa, an attempt at reconstruction should be carried out.

In the next chapter, Bakker and Cornil explain, with justification, that ureterosigmoidostomy is a good operation in a child, provided a satisfactory implant is achieved with a projecting nipple. They advocate Mathisen's method and this is well illustrated. They describe the ease with which a ureterosigmoidostomy can be converted to a colonic conduit, but some advice should be given that the original siting of the anastomoses should be planned with the possibility in mind of a subsequent conduit being formed at a later date.

A chapter on management of the neurogenic bladder is clearly the wisdom derived from a large experience with this condition. Zachary warns against the use of manual expression in the high pressure bladder or when there is gross reflux or when residual urine still remains after each effort at manual expression. The advice on trans-urethral resection of the bladder neck and external sphincter is limited and he makes the statement that trans-urethral resection results in a diverticulum of the urethra! (Clearly the writer feels happier with an open operation for sphincterotomy.)

There is a chapter on the electronic stimulation of the pelvic floor for urinary incontinence but, like most other writers, De Backer carefully avoids any anatomical or physiological explanation of how and what he is stimulating.

Johnston and Kulatilake describe the posterior urethral valve and the use of a simple auroscope, through which the valves can be destroyed. Here, in this chapter, the dilated, obstructed ureter is relieved by a high loop cutaneous ureterostomy, which has been a life saving measure for many of these babies, preventing the unhappy secondary complication of a pelvi-ureteric obstruction which can follow release of pressure within the distended tortuous ureter.

Rickham presents an erudite and concise review of malignant tumours, involving the genito-urinary tract. This chapter contains an excellent list of relevant references.

There is a refreshing chapter on the localisation of urinary tract infection, in which all the various tests for localisation of infection into upper or lower urinary tract are assessed and the writer has wisely come to the conclusion that, as yet, there is no simple way to determine, with any degree of confidence, the exact localisation of the bacteriuria.

The final chapter is a critical appraisal of the management of ureteric reflux, which illustrates clearly the swing of the pendulum over the past few years from the time when nearly all refluxing ureters were subjected to an anti-reflux operation to the present day, when a much more conservative approach is adopted.

We are all aware of the difference of opinion as to whether we should use the adjective "ureteral" or "ureteric", depending on which side of the Atlantic the book is published, but to find both words used in successive sentences on page 251 is a little distracting to the reader. Apart from this very minor inconvenience it was a most enjoyable book to read, and the publishers should be congratulated on the illustrations, the layout of the type and the whole presentation.

Although there are many other facets of paediatric urology which might have been included in this book, such as a review of the developments in endoscopic instruments, nevertheless this book demonstrates considerable depth of thought and knowledge by a group of outstanding experts in their particular subjects. The Editors have produced an excellent composite work, which all urologists and paediatric surgeons with an interest in paediatric urology would wish to read.

J. P. M.

Metabolic Bone and Stone Disease. By B. E. C. NORDIN. 1st Edition. Pp. viii+309, with 140 illustrations. Edinburgh and London: Churchill Livingstone. 1972. £5.00.

When the tragic early death of Paul Fourman deprived us of further editions of his book on calcium metabolism it was obvious that someone else must step into the breach. It comes as no surprise that his colleague at Leeds, Professor Nordin, has taken up the task. The book reflects Professor Nordin's spread of interest through metabolic

disease to the kidney with special attention to senile osteoporosis and renal calculi, but it is not just a personal account. Those who are accustomed to hearing Nordin argue his case against all opposition at medical research meetings may be surprised at how little his own views obtrude into a balanced review of the literature. None the less he is able to call on a very extensive experience in the field, well illustrated by the numerous diagrams he has borrowed from the previous publications of his group. He has packed a great deal of information into a very small compass and I found the book very readable in spite of thorough annotation with over 1,000 references, all of which are given in full in the end pages. I would thoroughly recommend the book to physicians, particularly those interested in metabolic disease in nephrology, but what is there in it for urologists? About an eighth of the book is devoted to renal calculi and this gives a succinct but thorough account of the subject. There is also a full chapter on renal bone disease which I found a very helpful summary of my own favourite topic. If it leaves out a few of the complexities and largely ignores the problem of dialysis bone disease, this will not disappoint many surgical readers because most descriptions of this confusing subject err on the other side and bury the few agreed facts in a welter of speculation. I am not sure now many urologists will buy this book for the sake of two excellent chapters but at least they should recommend it for the postgraduate library and borrow it. At £5, with art paper permitting good reproduction of radiographs, it is good value at today's prices and shouldn't bankrupt the Hospital Management Committee.

D. N. S. K.

Conferences and Courses

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A Week's Course in **SPECIAL ASPECTS OF UROLOGY** will be held from 24TH to 29TH SEPTEMBER 1973.

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Further information regarding the details of the course may be obtained from:

Mr N. O. K. GIBBON, ChM, FRCS,
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INDEX TO CURRENT UROLOGICAL LITERATURE

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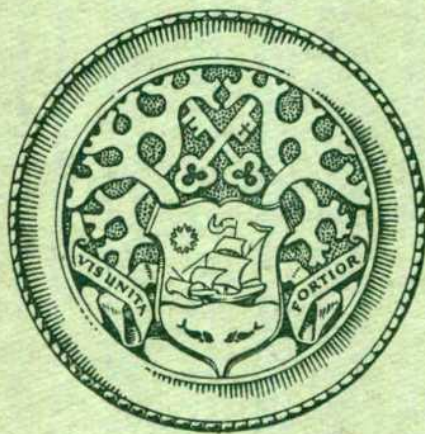
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- (1) *Postgrad med J.* (1971), (September Supplement), 47, 7.
 - (2) *Brit med J.* (1969) *i*, 541.
 - (3) Leading Article, *Brit med J.* (1969), *i*, 525.
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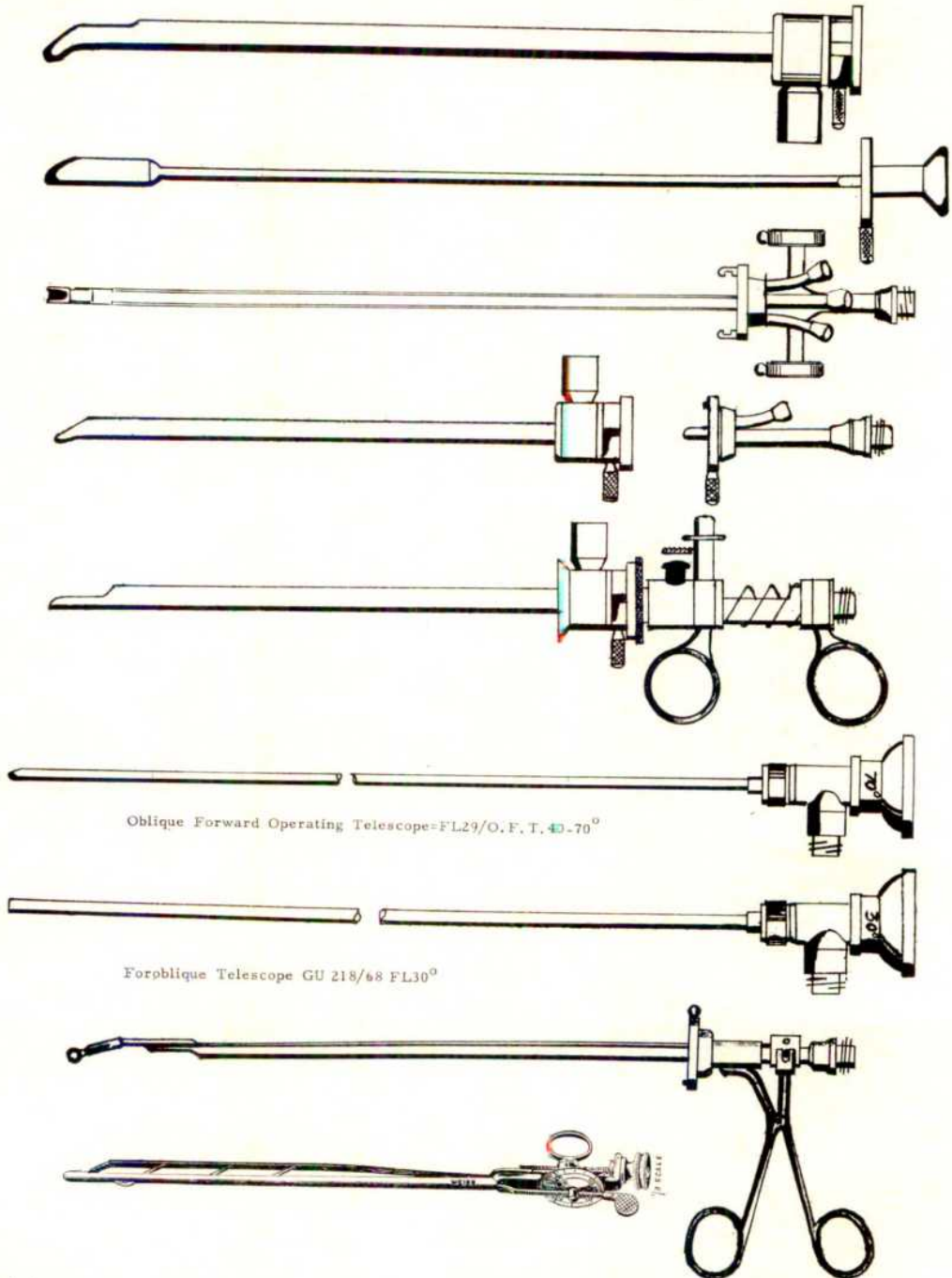
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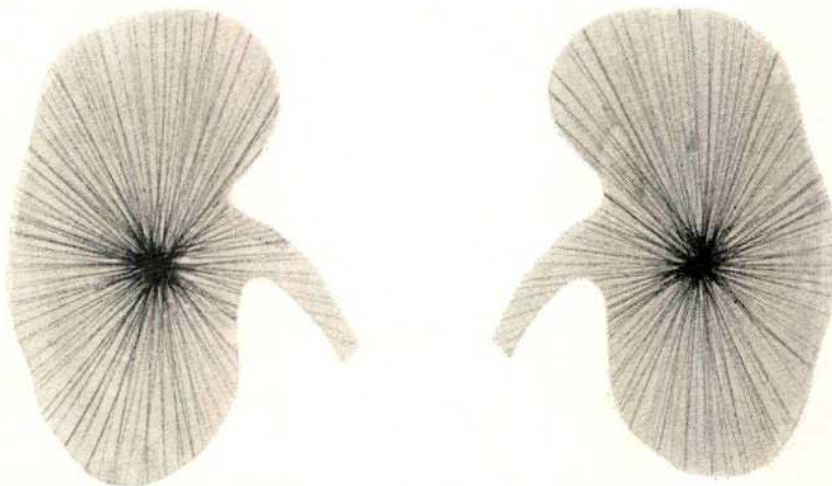


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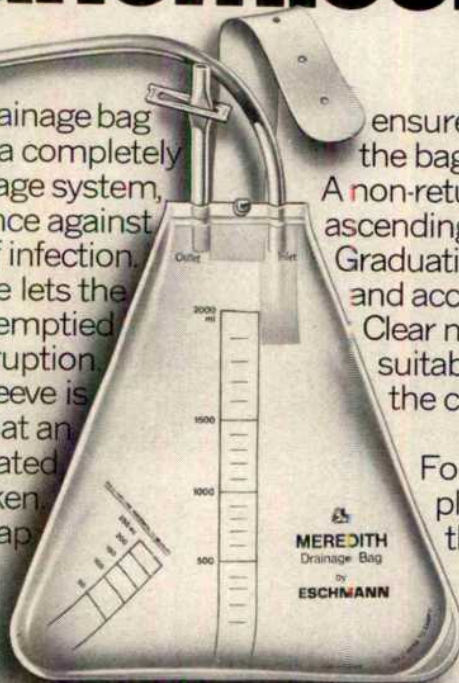
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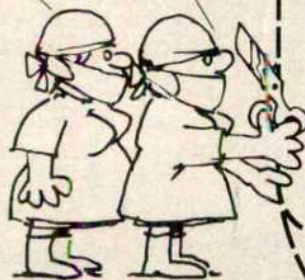
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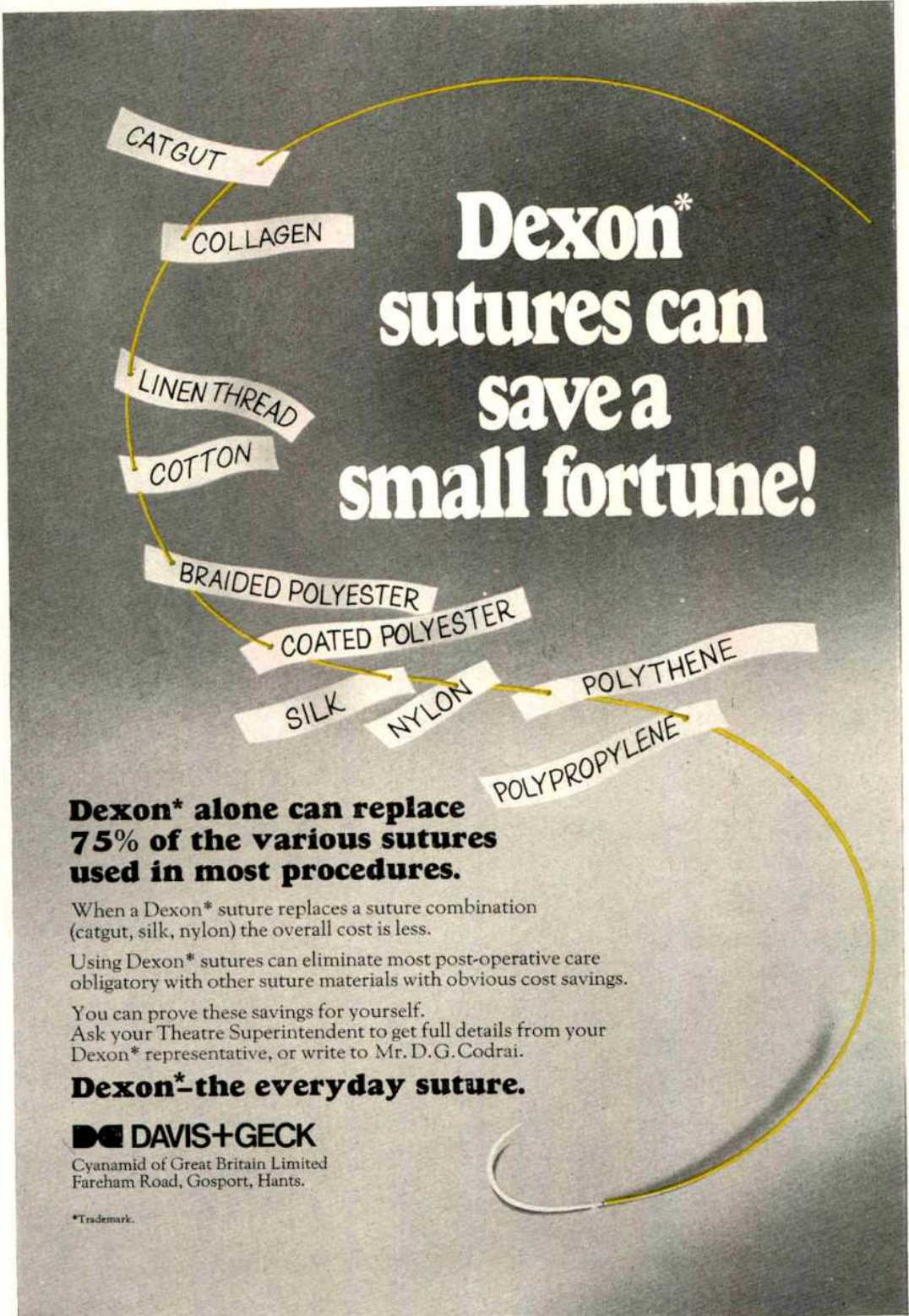
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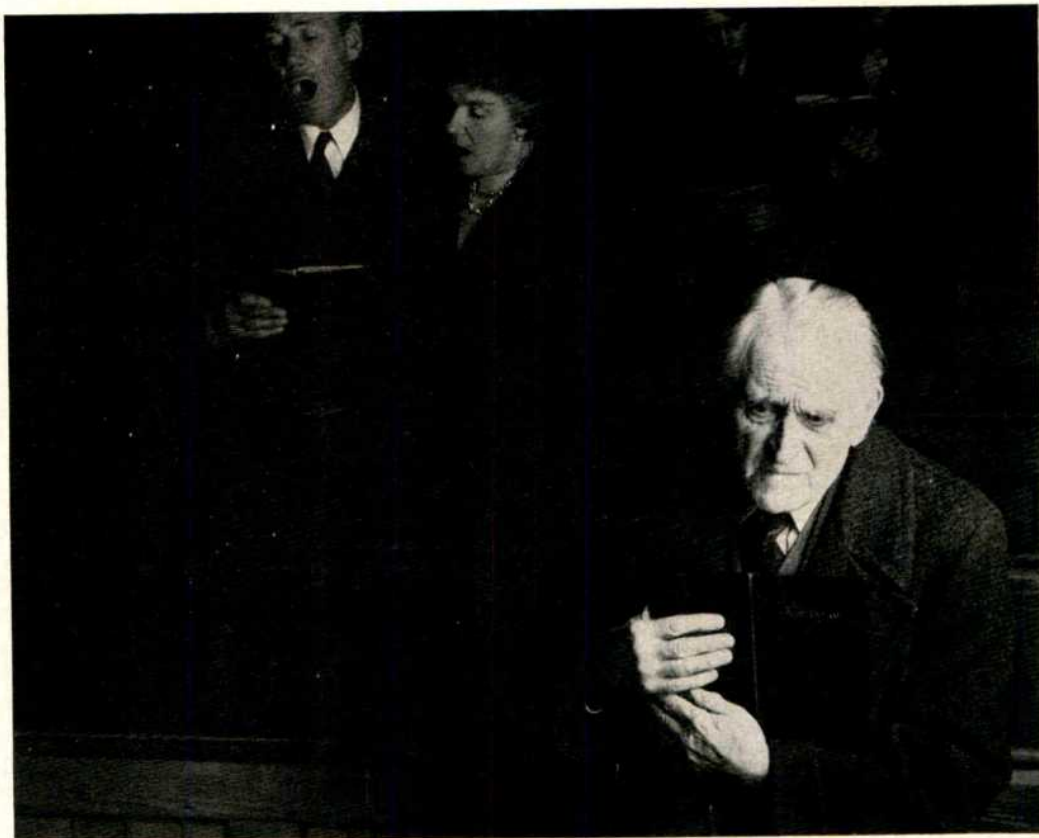
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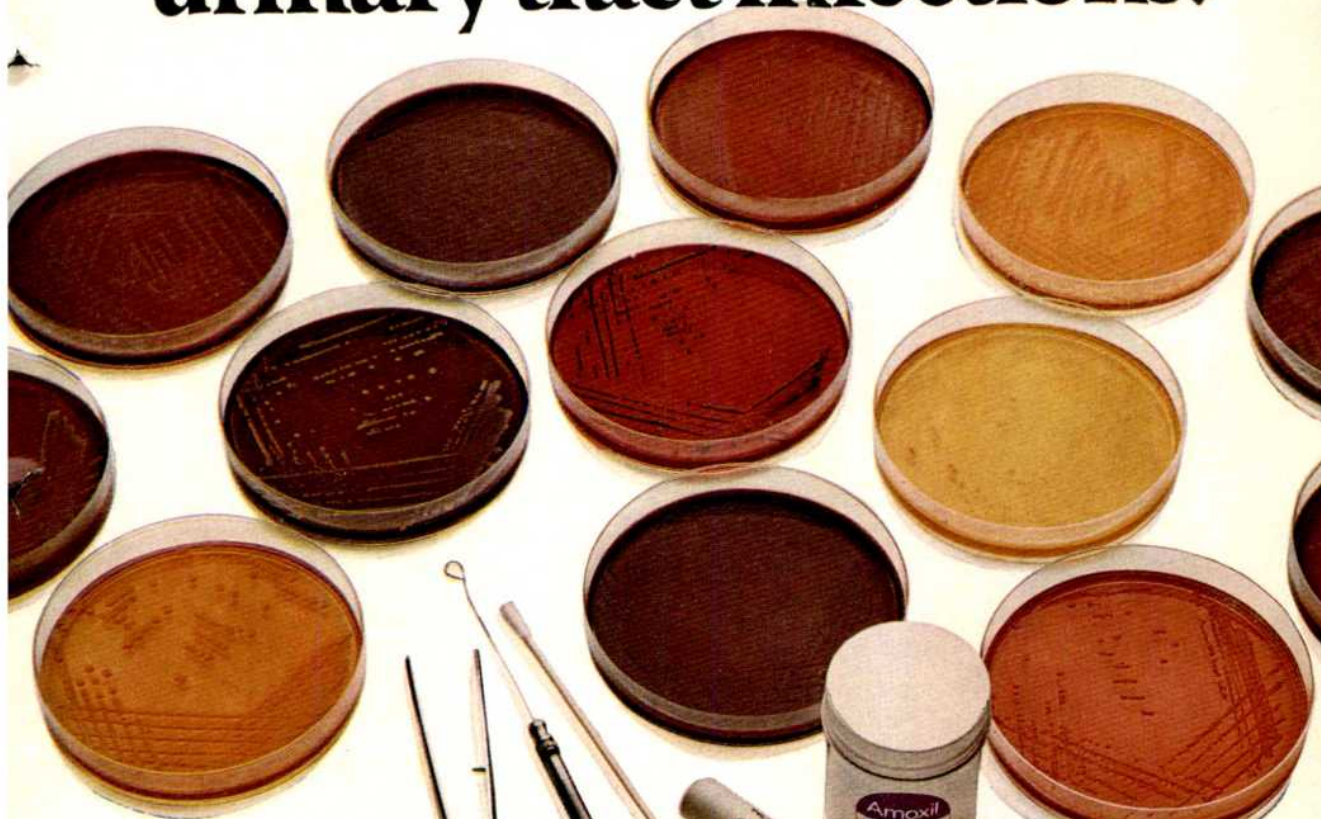


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1. Brit. Med. J., 1972, 3, 13.

2. Brit. J. Clin. Pract., 1972, 26, 341.

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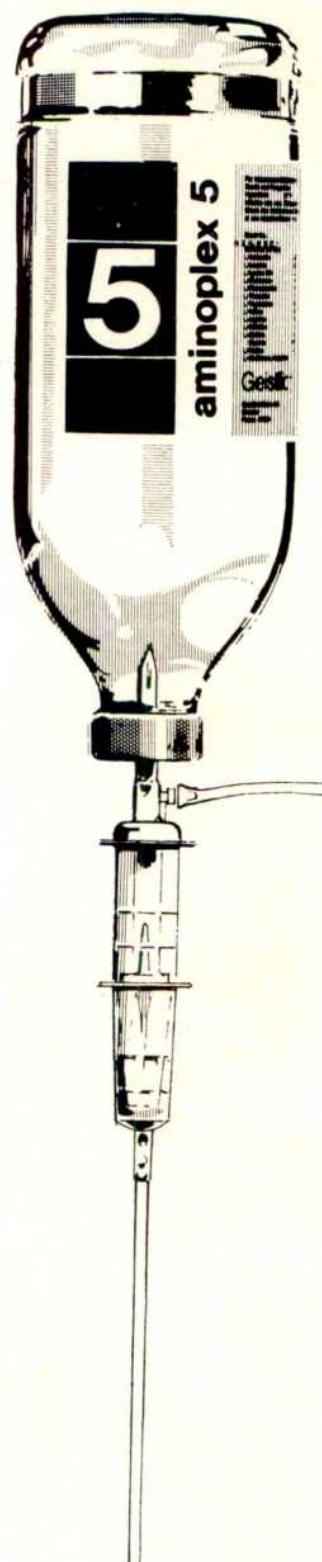
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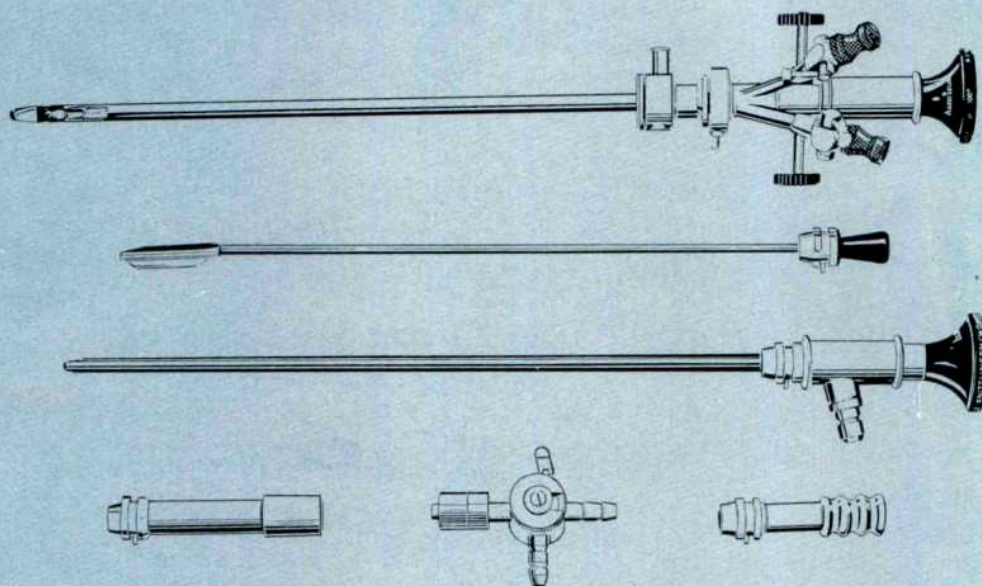
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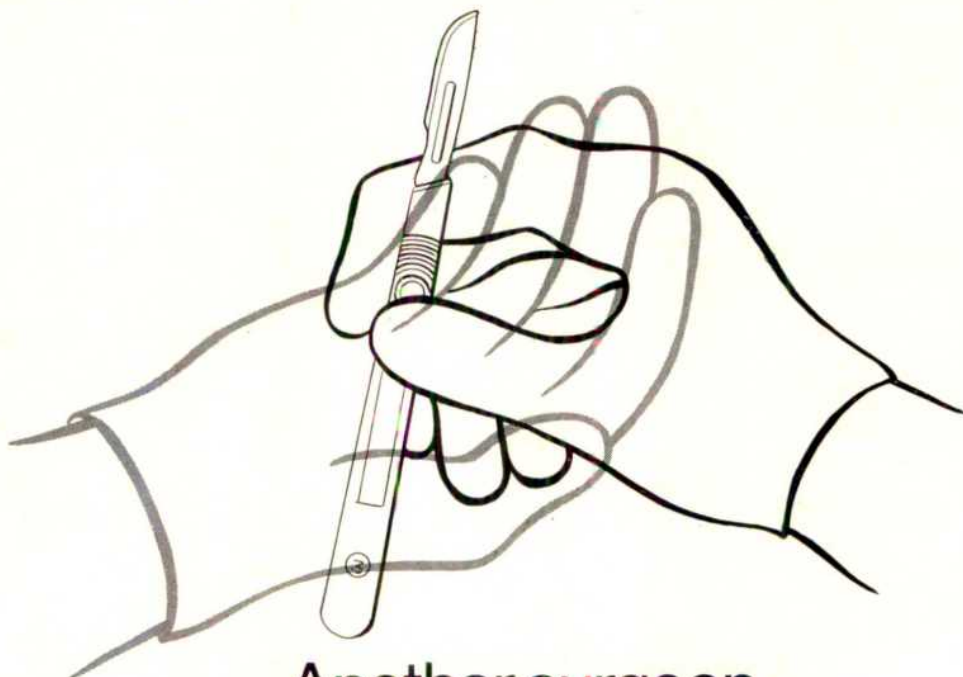


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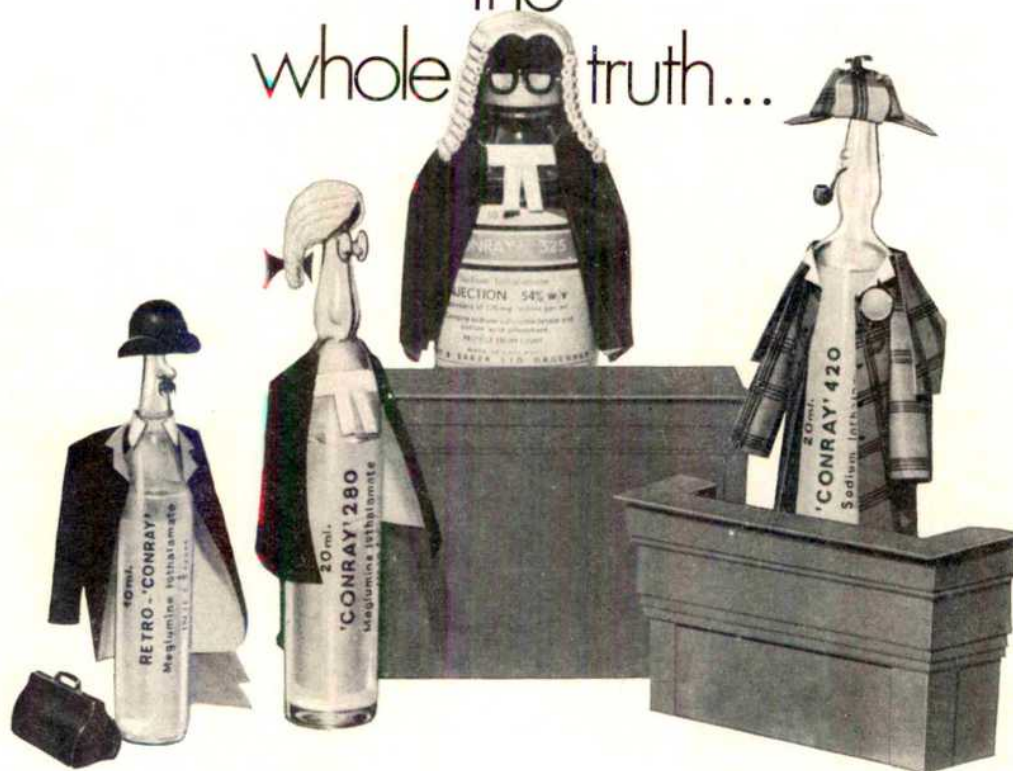
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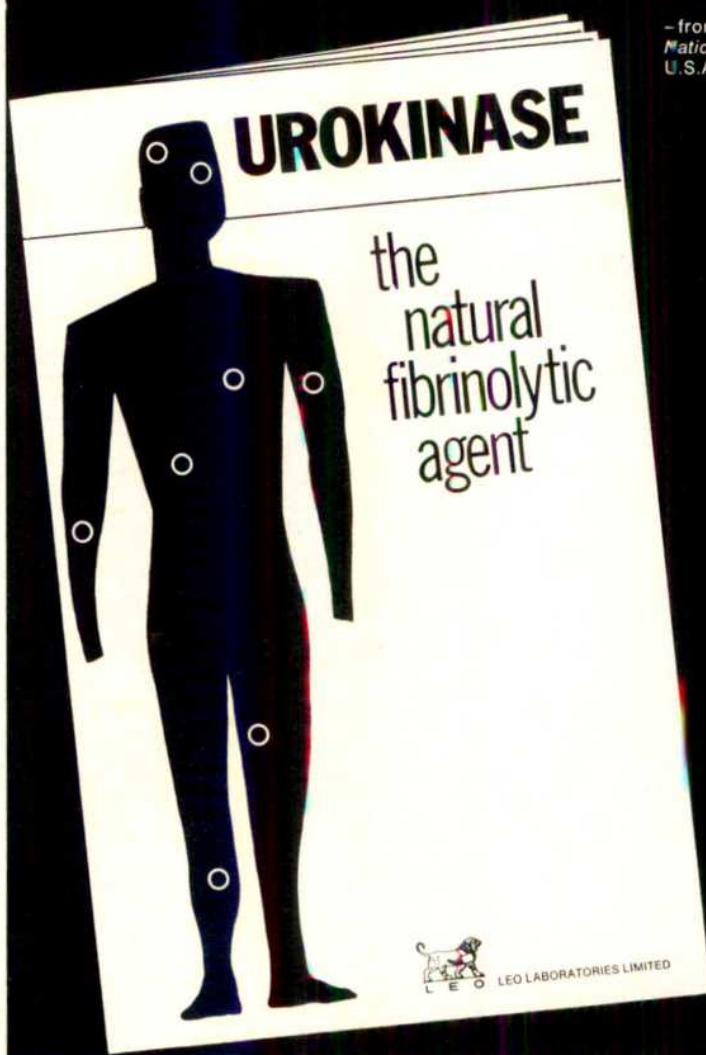


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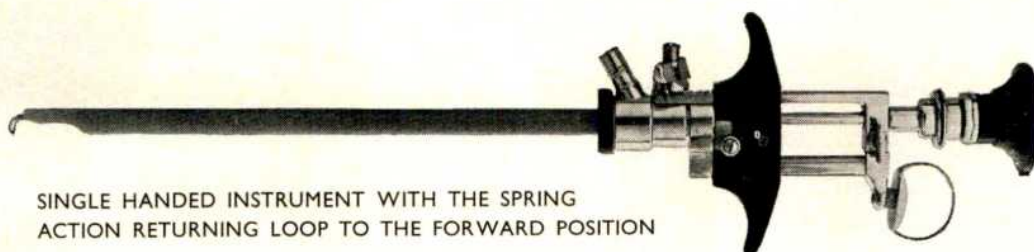
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P. A. POOLE-WILSON

St Thomas's Hospital, London, SE1 7EH

Urolithiasis is a well-recognised and common long-term complication of severe poliomyelitis, occurring in 26% to 43% of cases (O'Connor and Wiener, 1956; Riley and Knight, 1958; Sweet, 1958; Elliott and Todd, 1961.) This high incidence of stone formation has been related to the hypercalciuria resulting from immobilisation (Dunning and Plum, 1957; Rose, 1966), urinary tract infections (Sweet, 1958) and the high pH of the urine (Elliott and Todd, 1961). When a group of patients with severe sequelae of poliomyelitis were reviewed at the respiratory unit of the South Western Hospital, the development of urolithiasis was also found to be related to the form of respiratory assistance received by the patient, being more common in those treated by the tank respirator. This observation has not been previously reported in the literature and this paper presents the results of a detailed study.

Patients and Methods

The details of 61 patients, of whom 27 were directly observed in the South Western Hospital respiratory unit, were obtained by questionnaire. All had contracted poliomyelitis between 1945 and 1963 and had a present age range of 24 to 62 years. The average age of onset of poliomyelitis was 27 years. 34 were female and 27 were male.

Those admitted to the series of 61 patients had required respiratory assistance by means of the tank respirator or intermittent positive pressure ventilation (I.P.P.V.) for more than 16 hours of each day for at least the initial 3 months of their illness. These criteria for inclusion were arbitrary but formed a natural group of those with severe respiratory incapacity.

Immobility was assessed by establishing the extent of limb and body movements, 100% being total paralysis and 0% being normal. The number of urinary tract infections in each patient was impossible to assess absolutely, but a detailed history as to their frequency was obtained. Documented bacteriological confirmation was available only in the 27 patients attending the hospital. Urinary lithiasis was presumed if (i) an operation had been performed for that purpose, (ii) X-ray evidence was obtained or (iii) a stone had definitely been passed. The mode of respiratory assistance was determined by direct questioning. The results were analysed using a χ^2 test.

Results

All the 61 patients in this series had severe paralysis. Only 1 had less than 50% paralysis in the first 3 months of the illness and 43 (70%) had greater than 85% paralysis. At the present time, which is 9 years after the last patient developed acute poliomyelitis, 14 (23%) have less than 50% paralysis. No correlation was demonstrated between the severity of the paralysis at any time in this group and the form of respiratory assistance, the incidence of urinary infections or urolithiasis. At the present time 15 patients who developed stones, and 16 who did not, have more than 75% paralysis; 10 patients with stones and 18 without have less than 25% paralysis.

The vital capacity was obtained in 49 patients. Four patients had a vital capacity below 200 ml, 9 below 400 ml, 20 between 400 ml and 800 ml and 16 above 800 ml. No correlation existed

between the vital capacity on the one hand with either urolithiasis or with the form of respiratory assistance during the first year of the illness on the other. The form of respiratory assistance in relation to time is shown in Table I.

Table I

The Number of Patients and the Predominant Form of Respiratory Assistance in Relation to Time from the Onset of the Illness

Main Form of Respiratory Assistance	Time during illness		
	At 3 months	At 1 year	At present time
Intermittent positive pressure ventilator	21	15	8
Tank	40	39	13
Cuirass	0	3	16
Rocking bed or glossopharyngeal breathing	0	4	24

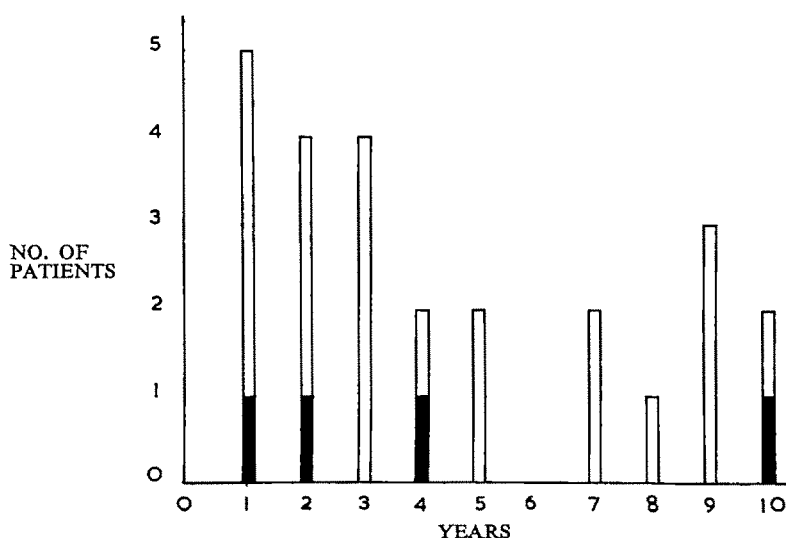


Fig. 1. The time after the onset of poliomyelitis at which a diagnosis of urolithiasis was first made. Darkened areas represent patients on I.P.P.V.

Urolithiasis and Respiratory Assistance

Urolithiasis occurred in 25 patients (41%). Stones were diagnosed by X-ray in 24 and by the passage of a stone in the urine in 1. Ten had required operations on account of urolithiasis and 4 underwent nephrectomy. The presence of stones was unrelated to vital capacity, the degree of immobility or the previous history of urinary infections. Figure I shows the period of time elapsing between the onset of poliomyelitis and the clinical manifestation of urinary stones.

A significant correlation existed between the form of respiratory assistance and the development of stones as shown in Table II. Thus at 3 months only 4 patients out of 21 on I.P.P.V. developed stones in contrast to 21 out of 40 using the tank respirator. These figures are statistically significant ($P < 0.014$). At 1 year, though fewer patients were needing respiratory assistance by tank or I.P.P.V., there is still a significant correlation ($P < 0.025$). At the present time the

numbers of patients are small. This association between the use of the tank and stone formation could not be explained in terms of differences in vital capacity, immobility or urinary infections.

Table II

The Development of Urolithiasis in Relation to the Main Form of Respiratory Assistance and Time from the Onset of the Illness

	Patients in Tank Respirator or on Intermittent Positive Pressure Ventilation (I.P.P.V.)					
	At 3 months		At 1 year		At present time	
	I.P.P.V.	Tank	I.P.P.V.	Tank	I.P.P.V.	Tank
Patients who developed stones at any time	4	21	3	21	1	7
Patients who have never developed stones	17	19	12	18	7	6
	P < 0.014		P < 0.025			

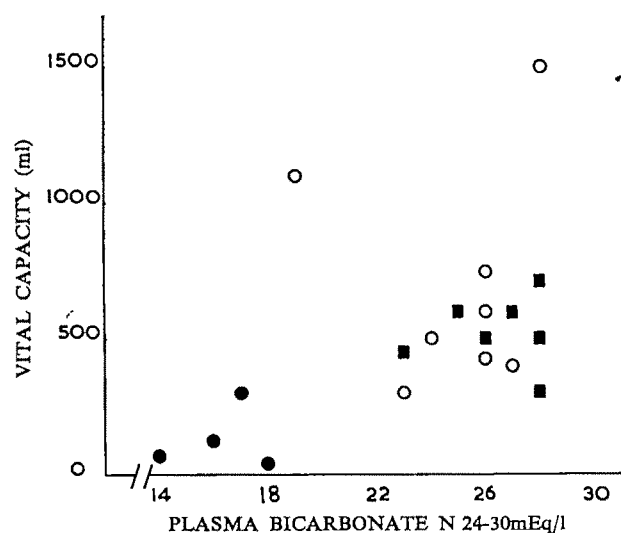


Fig. 2. The vital capacity is plotted against plasma bicarbonate. ● = I.P.P.V. and no urolithiasis. ○ = Tank respirator or cuirass and no urolithiasis. ■ = Tank respirator or cuirass and urolithiasis.

Biochemical Results

Biochemical investigations were available in only 19 patients. In the presence of normal renal function the plasma bicarbonate level is an indication of the chronic ventilatory state. Figure 2 shows plasma bicarbonate plotted against vital capacity in 19 patients. Of these, 7 had stones. Four, who were on I.P.P.V., had markedly low plasma bicarbonate levels ranging between 14 and 18 mmol/100 ml and did not develop stones at any time. The remaining 15 patients had bicarbonate levels between 19 and 28 mmol/100 ml. Of these, 7 developed urolithiasis. In 13 of these patients, 5 of whom had developed stones, plasma calcium, phosphate and alkaline phosphatase were normal.

Urinary Tract Infection

Urine infections were common. 23 patients had none, 17 had less than 1 per year, 18 had between 1 and 5 per year and 9 had more than 5 per year. No correlation was established between infection and the form of ventilation, and those in whom urolithiasis became manifest at a late stage of their illness (Fig. 1) did not have an increased frequency of infection. Of the 25 patients with renal stones, 8 had recurrent infections, and of these, 6 had persistent urolithiasis. 16 patients out of 36 without renal stones also had recurrent infections. Urinary infections were associated with urolithiasis only when stones were persistently present. The only factor with positive correlation with urinary tract infection was an increased incidence in the female. Thus, only 4 of 27 males had more than 1 infection in contrast to 14 out of 34 females who had more than 1 infection ($P < 0.025$).

Discussion

The patients described in this series had respiratory failure of such severity resulting from paralytic poliomyelitis as to require respiratory assistance by tank or I.P.P.V. for at least 3 months of their illness. These criteria for admission to the series were arbitrary but formed a natural division between those with mild and those with severe disease. This group of patients is unique in that only after 1945 did techniques for respiratory assistance become readily available, and following the introduction of vaccines the disease became rare after 1961; the methods of respiratory assistance used were the cabinet respirator (tank or iron-lung), the intermittent positive pressure ventilator (I.P.P.V.) and the cuirass. While the total number of such patients in the UK is unknown, in a recent extensive survey, 197 of 1,766 patients with poliomyelitis mentioned an impairment of breathing but only 4 allegedly suffered from total respiratory paralysis (Lee, 1965). The number of persons in Britain disabled by poliomyelitis was estimated at 12,000, and other series have suggested 1-2% of these would need respiratory assistance (Lassen, 1953; Kelleher, Medlock and Powell, 1956; Pejme *et al.*, 1959). Thus between 120 and 240 persons in Britain may have important respiratory impairment and since this group is extensively afflicted by paralysis it is most at risk with regard to the development of urolithiasis. 61 such patients are reported in this study.

Urolithiasis is a common complication of severe poliomyelitis and the incidence of 41% in this series is in agreement with that found in others (O'Connor and Wiener, 1956; Riley and Knight, 1958). Eight patients first developed stones between 7 and 10 years after the initial illness and in these patients hypercalciuria may not be an important factor since it rarely persists beyond 24 months (Dunning and Plum, 1957). Many other factors however are known to be relevant to stone formation, but the observation that urolithiasis is related to the form of respiratory assistance, being uncommon in those on I.P.P.V., has not been previously reported. Such a finding might have been explained by differences in those on the tank and I.P.P.V., in the degree of immobility, the incidence of urinary tract infections, or the presence of urinary stasis in the renal pelvis. However, none of these explanations can be sustained by the evidence available from this survey. All the patients were severely immobilised and urinary infection did not correlate with the form of respiratory assistance. Urinary stasis certainly occurs in both groups, but since the patients are equally paralysed and have similar physiotherapy and turning schedules, to postulate a difference in the degree of stasis is not reasonable.

Hyperventilation in patients on I.P.P.V. is difficult to assess objectively as these patients have notoriously small arteries and strongly dislike arterial puncture which is justified only when respiratory embarrassment makes the information of clinical importance. Nevertheless, venous plasma bicarbonate levels in the absence of renal failure give an indication of the chronic state of ventilation and suggest, being low, that patients on I.P.P.V. are overventilated. Elliott and Todd (1961) have shown that alterations in chronic ventilation in these patients do not affect

urinary pH, a finding which would be expected, and that in patients with severe poliomyelitis the urine pH tends to be raised due to an absence of muscle metabolites. Thus, if hyperventilation not only correlated with the absence of stone formation but was also directly responsible for the decreased incidence, the mechanism cannot be of renal origin, but could be due to an effect of acid-base balance on calcium metabolism itself. This hypothesis would be supported by this study.

Urinary tract infections were common in the whole group. Although infection was not associated with either the mode of respiratory assistance or the presence of stones in the urinary tract, there was a higher incidence in the female sex suggesting that the anatomy of the female urethra was an important factor, and these findings correspond with the known sex distribution of urinary tract infections.

Summary

25 (41%) patients, in a review of 61 patients with severe respiratory poliomyelitis, developed urolithiasis.

There was a significantly increased incidence of stone formation in the urinary tract amongst those using the tank respirator when compared with those on intermittent positive pressure ventilation (I.P.P.V.).

It is suggested that overventilation of patients on I.P.P.V. protects against urolithiasis by a direct action on calcium metabolism.

No correlation existed between the occurrence of urolithiasis and either urinary tract infection or the degree of immobility.

I would like to thank Mr R. W. Lloyd-Davies and Dr G. T. Spencer for their advice, assistance and encouragement.

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Uric Acid Lithiasis in the Ileostomy Patient

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The incidence of urinary lithiasis is unusually high in patients who have had colonic resection followed by ileostomy for inflammatory bowel disease. Reports in the literature show the frequency of calculi in ileostomy patients to range from 7.4% (Bennett and Jepson, 1966) to 12.5% (Deren *et al.* 1962). This incidence is greatly in excess of that found in the general population. In the majority of their patients the calculi were found to consist of uric acid.

Case Reports

Case 1. Mr R. B., aged 45 years. This patient was admitted to the Urology Service in January 1971 with left renal colic. Examination of the urinary sediment showed the presence of 10-30 rbc per hpf and 0-1 wbc per hpf. An intravenous pyelogram performed on admission revealed dilatation of the left ureter down to the pelvic brim. No opacities were seen in the course of the left ureter. Subsequent cystoscopy and basket extraction yielded golden yellow calcareous material from the left ureteral orifice. Analysis revealed this to be composed of urates and uric acid. Large thin wafer-like stones were also found in the bladder. These were crushed and on analysis proved to be identical in composition to the ureteral calcareous material. The patient had a past history of ulcerative colitis treated by subtotal colectomy and ileostomy in August 1964, and followed later by proctectomy in November 1965. Prior to the current admission in January 1971 there had been 3 other admissions for left renal colic respectively, in February 1968, February 1970, and November 1970. On each occasion non-opaque calculi were extracted from the left ureteral orifice which upon analysis were shown to consist of urates and uric acid. The patient had not been on steroid therapy during the above period.

Of 8 estimations of urinary pH performed in the period since the ileostomy, 7 showed the pH to be 5.5 or less. No value higher than pH 6.0 was ever obtained. Urinary uric acid excretion was found to be normal (mean 486 mg per day, range 357-588 mg per day). Urine volumes on high fluid intake ranged from 1580 cc to 2100 cc per day with a mean of 1860 cc per day. Of 7 serum uric acid estimations performed in the above period, only 1 reached the upper level of normal for this laboratory of 8 mg % (mean 7.5 mg, range 6.3-8.0 mg %). Of 6 blood estimations in the above period serum electrolytes were at all times normal. Mean BUN was 13.1 mg % with a range 9-15 mg %. Mean serum creatinine was 1.5 mg % with range of 1.3 to 2.1 mg %.

Case 2. Mrs H. M., aged 38 years. This patient was admitted to the Urology Service in December 1970 with a 4-month history of left flank pain. Examination of the urine sediment showed 50-100 rbc per hpf and 3-5 wbc per hpf. An intravenous pyelogram performed on admission revealed dilatation of the left ureter down to its lower one-third. No opacities were seen in the course of the left ureter. A retrograde ureterogram confirmed the presence of a non-opaque stone in the left lower ureter. A left lower third ureterolithotomy was performed; the calculus measuring 2 x 1 cm yielded urates, uric acid and ammonium upon analysis. The patient had a past history of Crohn's disease for which subtotal colectomy and ileostomy were performed in August 1966, followed by a proctectomy in February 1967. The patient had been on continuing therapy with prednisone 5 mg t.i.d. because of the development of further ileal disease.

Of 8 estimations of urinary pH performed in the period since the ileostomy, 6 were pH 6.0 or less. No values higher than pH 6.5 were obtained. Uric acid excretion was found to be normal in 6 estimations (mean 444 mg % per day, range 294-800 mg per day). Urine volumes were low with a mean of 800 cc per day and a range of 680-1250 cc per day.

Of 6 serum uric acid estimations on the above period only 1 exceeded the normal level of 8.0 mg % (mean 6.5 mg % and range 4.5-8.1 mg %). This high level coincided with an elevation of serum creatinine to 2.1 mg %. Serum electrolytes at times were abnormal with the lowest CO₂ level recorded being 18.0 mEq per litre. Mean BUN was 24.5 mg % with a range of 13-39 mg %. Mean serum creatinine was 1.65, 1.3-2.1 mg %.

¹ Read at the Annual Meeting, Canadian Urological Association, Montreal, Quebec, May 1972.

Comment

Uric acid lithiasis accounts for approximately 5 to 10% of all urinary calculi in the North American environment. The predisposition to uric acid calculus formation is considerable in hyperuricaemic states such as are found in idiopathic hyperuricaemia, gout, and myeloproliferative and neoplastic disorders. Conditions which cause hyperuricosuria without hyperuricaemia similarly predispose to calculus formation. The latter situation may result from the use of several drugs including salicylates, steroids, probenecid and phenylbutazone. In the variety of uric acid calculus in which neither hyperuricaemia nor hyperuricosuria exists there is found a consistently acid pH urine which favours the precipitation of uric acid. This variety seems to be prevalent amongst Jews and Italians (Melick and Henneman, 1958).

In the ileostomy patients described it is noted that there was no evidence of hyperuricosuria nor evidence of persistent hyperuricaemia. The main factors favouring the deposition of uric acid calculi in the urinary tract of the ileostomy patient appear to be (1) oliguria, (2) acid urine, (3) urinary infection.

Oliguria. A low urine volume favours the precipitation of relatively insoluble substances by increasing their concentration in the urine. In addition, the slow flow of urine favours crystallisation of potentially insoluble substances. The presence of an ileostomy creates the problem of an abnormal source of fluid loss. Gallagher, Harrison and Skyring (1962) have documented the extent of this loss in 20 ambulatory ileostomy patients and have found it to range from 380 to 1,500 cc per day (mean 690 cc per day). This abnormal water loss in itself is a stimulus for the renal water conservation mechanism and leads to oliguria.

The ileostomy contributes even further to the problem as Bennett and Jepson (1966) and Gallagher *et al.* (1962) have demonstrated in studying the sodium loss in the ileostomy fluid. The latter found these to be in the range of 44-197 mEq per day (mean 85 mEq per day). The daily potassium loss was not appreciably greater than that found in normal stool except if ileostomy diarrhoea were occurring in which case the concentration rose to as high as 40 mEq per litre. This loss of cation is accompanied by a considerable bicarbonate loss.

Measurements of total body water and total exchangeable sodium by Clarke *et al.* (1967) have demonstrated that the extent of this water and sodium depletion in apparently healthy ileostomy out-patients can be quite marked.

They demonstrated a mean reduction in total body of water of 11% and in total exchangeable sodium of 7% when compared with controls.

Gallagher *et al.* (1962) have studied the urinary volumes and urinary sodium excretion in the group of 20 ileostomy out-patients. The mean daily urine volume was 970 cc (mean for the control group was 1,410 cc). Seven of their 20 patients had a daily urine volume of less than 600 cc. The mean daily urine sodium excretion of the ileostomy group was 70 mEq per day (range 1-250 mEq per day) compared to a mean for healthy controls of 180 mEq per day (range 97-376 mEq per day). 15 ileostomy patients excreted less sodium than the lowest daily sodium output of the control group. The state of hydration of these patients already described as being precarious, is subject to further deterioration as a result of rather frequent episodes of ileostomy diarrhoea and small bowel obstruction. These episodes, albeit transient, may be of sufficient duration to permit precipitation of uric acid and the beginning of calculus formation.

Acid Urine. The solubility of uric acid in urine is critically affected by pH. At pH 5 as little as 8 mg per 100 cc urine is dissolved whereas at pH 7, 158 mg per 100 cc is dissolved (Grossman and Nugent, 1967). The pH of the urine was measured in 15 healthy ileostomy patients by Clarke and McKenzie (1969). The mean 24-hour urinary pH was found to be 5.1 (compared to pH 6.2 for the control group).

The tendency toward an acid urine in the ileostomy patient is caused by several factors. The

excessive loss of bicarbonate in the ileostomy patient is partly compensated by extra bicarbonate reabsorption in the kidney. In addition, the sodium deficit leads to increased sodium reabsorption which takes place partially in exchange for hydrogen in the distal convoluted tubule. Thus, an increasing hydrogen ion secretion is a mechanism for increasing sodium reabsorption. If hypokalaemia co-exists, as it frequently does, hydrogen ion secretion is further facilitated, leading to an even more acid urine.

Infection. Urinary tract infection has been incriminated in the pathogenesis of calculi in several ways. Tissue debris or bacterial clumps may be the nidus for the crystallisation process. In the case of phosphatic and mixed calculi which are sometimes observed in the ileostomy patient, the pH increasing effect of urea-splitting organisms is probably an aetiological factor. In the case of uric acid calculi only the nidus theory need be invoked. Of 13 patients with uric acid calculi described by Deren *et al.* (1962), 9 had urinary tract infections. Thus the importance of infection ought not to be overlooked. Certainly, there are ample reasons why infections of the urinary tract might occur. The use of indwelling catheters, the frequent presence of neurogenic bladders created by pelvic surgery are important factors in its pathogenesis. In the 2 patients described, an alkaline urine with pH 8 was readily obtained with sodium bicarbonate 1,200 mg t.i.d. in the case of H. M., and with potassium citrate $\frac{1}{4}$ teaspoon t.i.d. in the case of R. B. Attempts to increase oral fluid and salt intake in the case of H. M. in order to increase urine volume resulted in ileostomy diarrhoea despite the use of diphenoxylate—HCL atropine (Lomotil) and codeine. In addition, R. B., in view of his history of recurrent uric acid calculi, was treated with allopurinol 200 mg. t.i.d. to reduce urinary uric acid excretion.

The incidence of uric acid calculi in the ileostomy patient is distressingly high so that energetic measures appear justified to deal with this entirely preventable complication even before the first calculus episode occurs. The matter of prevention is made even more urgent by the observation in our own case R. B. that recurrence of calculi is frequent. A high incidence of recurrence was also observed by Bennett and Jepson (1966) as well as by Deren *et al.* (1962). A high fluid and salt intake is advised to prevent oliguria, with care being taken to drink fluid prior to retiring to reduce overnight dehydration. Regrettably, some patients tolerate excessive salt and water poorly and develop diarrhoea.

It is desirable also to alkalinise the urine as this markedly increases the solubility of uric acid. Alkalinisation can usually be easily attained by the ingestion of sodium bicarbonate, potassium citrate or acetazolamide (Diamox). Bennett and Jepson (1966), however, have noted that some patients are exceedingly refractory to alkalinisation. The urinary pH should be monitored by the patient to ensure persistent alkalinisation. One ought to aim for a urinary pH of 6.5 or greater.

In addition, allopurinol has been demonstrated to reduce significantly uric acid stone formation in uric acid stone formers (Godfrey and Rankin, 1969). The drug is relatively non-toxic and should be administered to those patients in whom alkalinisation or creation of a high urine flow has been a problem. It would appear to be definitely indicated if the above regimen has failed to prevent uric acid stone formation. The dosage should be regulated according to the levels of uric acid in a 24-hour urine sample.

Ileostomy diarrhoea may be reduced and controlled by attention to aggravating dietary factors and the exhibition of agents such as diphenoxylate HCL-atropine (Lomotil) and codeine to control the frequency and looseness of motions. Occasionally, revision of a partially obstructed ileostomy may be necessary.

The diagnosis of uric acid calculus is frequently delayed if haematuria is absent because the ileostomy patient may have a multitude of pains so that a low grade renal pain can go unrecognised. For these reasons it seems advisable to study the urinary tract by intravenous pyelogram annually. A plain film and a 20-minute exposure would yield the maximum information with least radiation dosage.

Summary

Two cases of uric acid lithiasis in ileostomy patients are presented.

The aetiology of stone formation in these patients is reviewed.

Suggested measures to prevent and treat this tendency are discussed in the light of current literature on the subject.

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Unilateral Nephrectomy and Hypertension

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In 1934, Goldblatt produced sustained hypertension in the rat by unilateral renal ischaemia and reversed it by unilateral nephrectomy. Since then a large amount of both experimental and clinical evidence has supported these observations. Most named renal diseases have been incriminated as a cause of hypertension in man but the success of unilateral nephrectomy when carried out for the treatment of hypertension has varied from 10% to 70% and the figure usually quoted is 30% (Smith, 1956; Brown *et al.*, 1960; Kincaid-Smith, 1961; de Bakey *et al.*, 1964; Breckenridge *et al.*, 1967; Hunt *et al.*, 1970; Woods and Williams, 1971; Stockigt *et al.*, 1972).

Because of these varying reports there now exists considerable doubt as to whether or not unilateral nephrectomy is worthy of serious consideration in the treatment of hypertension. This doubt has become more prevalent with the availability of efficient anti-hypertensive drugs. In this paper, we have examined a group of patients with hypertension in whom unilateral nephrectomy was carried out for a variety of pathological conditions; the investigations used to study these patients, the long-term follow-up and the factors that influenced the results are presented.

Patients

47 hypertensive patients were studied; 46 were treated by unilateral nephrectomy and 1 by partial nephrectomy. There were 21 females and 26 males and their ages ranged from 15 to 63 years. 35 (73%) were receiving large doses of anti-hypertensive drugs before operation. All of the patients underwent detailed clinical assessment and blood pressure observations were made 4-hourly for several days. The mean preoperative systolic blood pressure was 217 ± 26 mm Hg in the male and 221 ± 30 mm Hg in the female; the mean diastolic blood pressure was 133 ± 6 mm Hg in the male patients and 131 ± 14 mm Hg in the female (Fig. 1). Grade 0 retinopathy was recorded in 10 patients, grade 1 in 10, grade 2 in 12 and grade 3 in 13; malignant hypertension was present in 2.

Urine was examined for protein, infection, vanillyl mandelic acid and catecholamines, and urine concentration tests were carried out. Blood urea and electrolytes, serum creatinine, creatinine and/or urea clearances were also determined. Chest X-rays, with special reference to heart size, electrocardiography and intravenous pyelography were instituted; aortography and selective renal angiography were done in 34 patients and differential renal function studies (Graber and Shackman, 1956) in 26 (Table I).

Renal ischaemia was present in 16 (Table II), hydronephrosis in 10, chronic pyelonephritis in 9, tuberculosis in 5, adenocarcinoma in 5 and hypoplasia in 2 patients. In a majority of patients, and excepting those with malignancy, the control of hypertension was the principal indication for nephrectomy.

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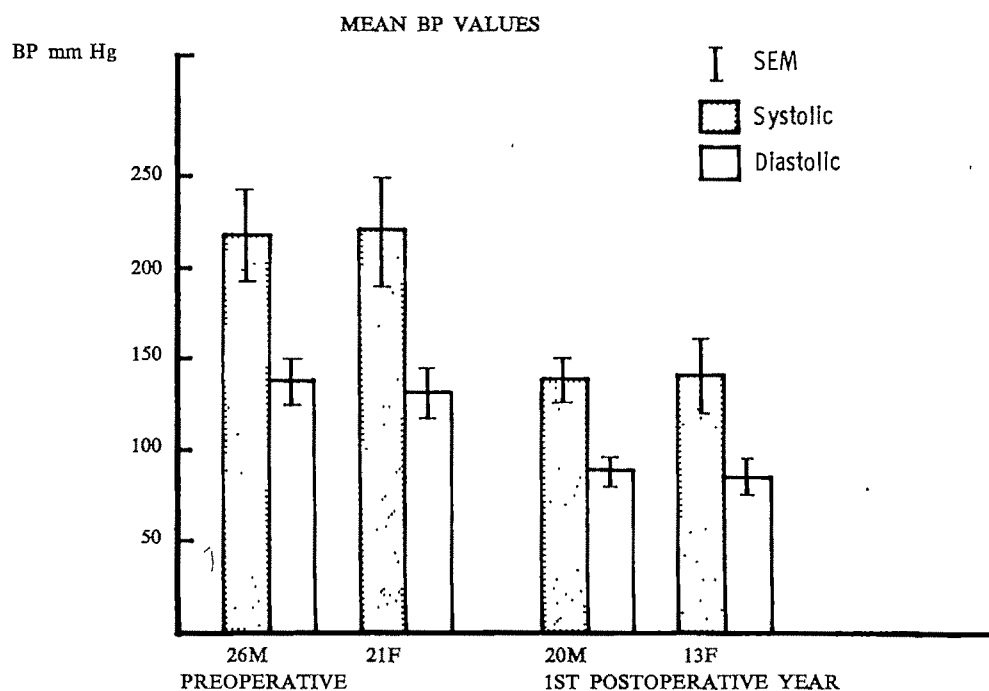


Fig. 1. Preoperative and postoperative blood pressure in 47 patients (SEM = standard error of the mean.)

Table I

Methods of Investigation in Patients with Hypertension and Unilateral Renal Disease

Pathology	No.	I.V.P. with Non-function or Poor Function	Differential Arteriogram	Studies
Renal ischaemia	16	2	15	12
Hydronephrosis	10	8	5	4
Chronic pyelonephritis	9	6	6	8
Tuberculosis	5	5	2	—
Renal cell carcinoma	5	5	4	—
Hypoplastic kidneys	2	2	2	2
Totals	47	28 (59%)	34 (72%)	26 (55%)

Table II

Lesions causing Renal Ischaemia

Arteritis of renal artery	2	Thrombosis of main renal artery	2
Fibro-elastic thickening	1	Renal infarct	1
Renal artery stenosis (atheroma)	6	Thrombosis of polar artery*	1
Aneurysm of renal artery	3		

* Partial nephrectomy.

Results

Of the 47 patients, 15 have been followed for 7 years and 1 for 16 years. The response to surgery was assessed by casual sitting or lying blood pressures taken in out-patient clinics. Two levels of success were recorded; complete success was claimed when the diastolic blood pressure did not exceed 90 mm Hg and the systolic 140 mm Hg $\pm$ 20 and partial success was claimed when the diastolic blood pressure was between 91-110 mm Hg. Since the proportion of partial successes

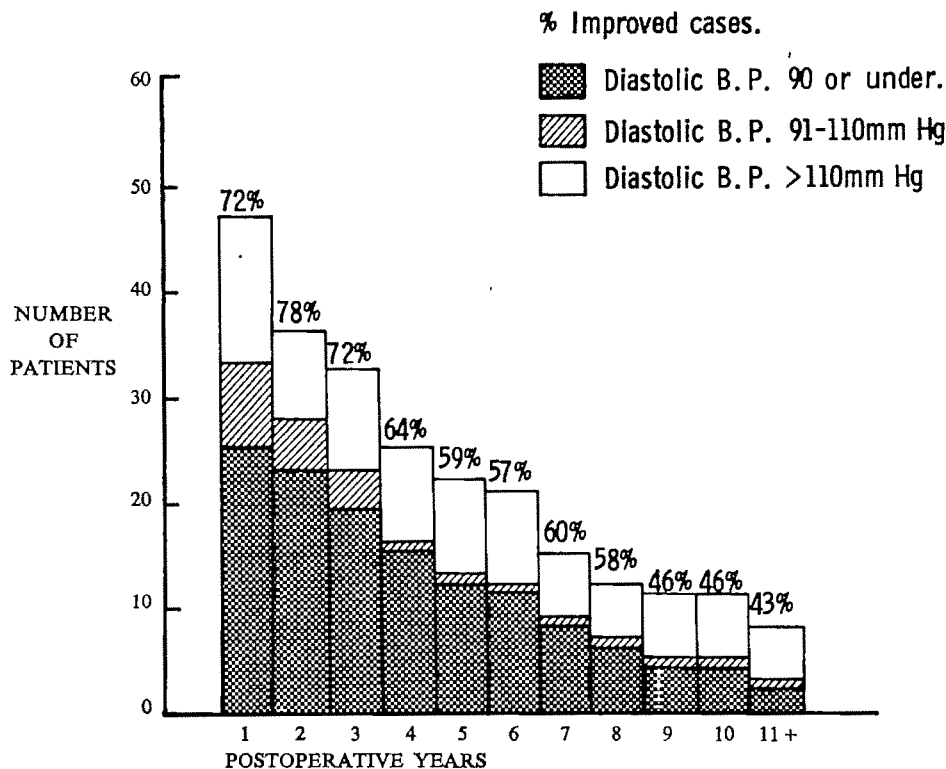


Fig. 2. Results of surgical treatment for hypertension. The proportion of improved cases (per annum follow-up) are shown at the top of each column.

was small (Fig. 2) the results in all patients with a diastolic blood pressure of less than 110 mm Hg (without drugs) are referred to as normotensive in this series. Two examples of patients followed for 10 and 16 years are shown in Figures 3 and 4.

The results show that 33 of the 47 patients followed at 1 year (Fig. 1) and 9 of the 15 that were followed-up for 7 or more years remained normotensive (Fig 2). Two patients with malignant hypertension had normal blood pressures up to 3 and 4 years after nephrectomy with reversal of the retinal changes. Four patients who died from myocardial infarction at 1, 3, 4 and 6 years after nephrectomy remained normotensive up to the time of their death; 2 had had malignant hypertension. Two others who remained normotensive died from cancer after 4 years. One patient with analgesic nephropathy failed to respond to nephrectomy and died from uraemia after 6 years.

Control of the hypertension was achieved after nephrectomy irrespective of whether the patients were older or younger than 40 years of age, but the failure rate was higher in those over 40. Thus, at the end of 1 year there were 5 failures (23%) in the group of 22 patients under 40,

whereas there were 9 failures (36%) in the 25 over 40. At the end of 5 years, 2 of the 11 patients under 40 had failed (18%) whereas there were 7 failures (63%) in the 11 patients over 40. In patients with left ventricular hypertrophy, as seen on chest X-rays and/or electrocardiograms,

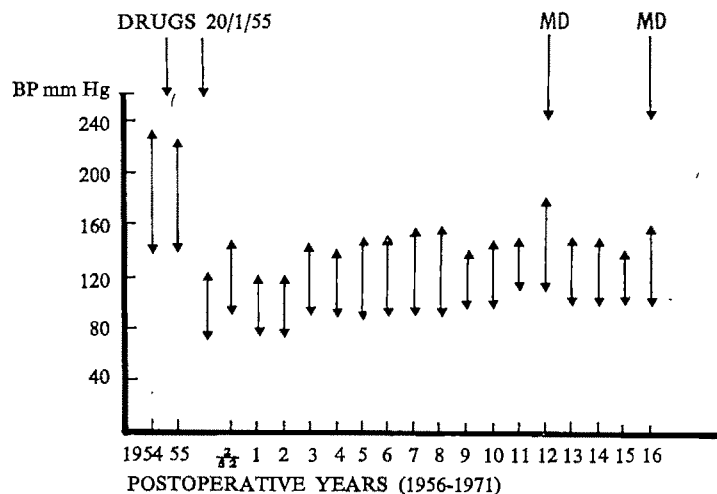


Fig. 3. 47-year-old male with hypertension, grade 3 retinopathy and left ventricular hypertrophy who received no antihypertensive therapy in the preoperative period. Left nephrectomy for renal artery stenosis with shrunken kidney on 25th August 1960. Normal blood pressure maintained during 10 year follow-up.

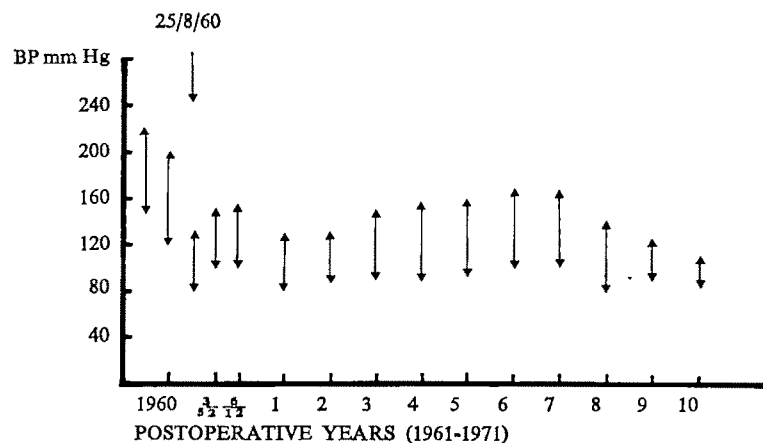


Fig. 4. 33-year-old male with hypertension, grade 1 retinopathy and normal heart size received Reserpine 0.5 mg daily to control his blood pressure. Following right nephrectomy in 1955 for chronic pyelonephritis normal blood pressure was maintained for 12 years. In 1967 the BP was 180/110 mm Hg and good control was obtained with methyl dopa (MD). Further investigations at this time were normal.

nephrectomy was followed by normotension in 64% of cases at 1 year and 53% at 5 years; in those with normal heart size, all remained normotensive for up to 5 years.

There was no statistical correlation between preoperative blood urea values (mean $32 \text{ mg} \pm 9 \text{ mg} \%$ range 20-60 $\text{mg} \%$) and the effect of nephrectomy on the hypertension ($P < 0.05$).

However, the response seemed to be equally effective whatever the nature of the primary renal disease. When hypertensive changes were present in the removed kidney, 43% improved after nephrectomy but when hypertensive changes were absent from the removed kidney, 67% remained normotensive for 5 years (the difference in response is however, statistically significant only at the end of the 1st year because the numbers are small $\chi^2 = 5.37$, $0.01 < P < 0.05$).

Although nephrectomy did not have a long-term beneficial result or normotension was never achieved in 21 patients (7 of whom had recurrence 2-12 (mean 6) years later), the subsequent requirement of hypertensive drugs was reduced at least by half in 11.

Discussion

Our results show that 60% of carefully selected patients with severe hypertension and unilateral renal disease can be cured by nephrectomy alone up to 7 years. This compares favourably with previous success rates of 10%-70% for unilateral nephrectomy in hypertension. The definition of success or cure must include reference to an adequate period of follow-up; two-thirds of the present series have been followed for a minimum of 3 years and one-third have been followed for 7 years. The dividing line between normotension and hypertension is a source of continuing disagreement in the medical world (Pickering, 1968). In this report the division for complete success was a diastolic blood pressure of 90 mm Hg or less while the few with a diastolic blood pressure of 91-110 mm Hg have been rated as partial successes since stable values of this order without drug treatment must also be considered a good response to surgery.

Patients under 40 years of age are said to be more likely to respond to surgery (Kincaid-Smith, 1961; Pickering, 1968; Johnson and Myers, 1971), and this has been our experience; 82% of our patients in this age group remained normotensive up to 5 years.

All of our patients with a normal heart size remained normotensive up to 5 years, but in those with left ventricular hypertrophy only half were improved. We have confirmed an observation made by Pickering (1968) that when hypertensive changes were not found in the removed kidneys, the result of nephrectomy was significantly better than when hypertensive changes were present. Indeed an important factor in the 30% initial failure rate seemed to be the presence of such changes; other factors were diseases in the contralateral kidneys, advancing age and long duration of hypertension evidenced by presence of left ventricular hypertrophy (Kincaid-Smith, 1961; Pickering, 1968; Johnson and Myers, 1971). In 7 patients with recurrent hypertension after nephrectomy there were hypertensive changes in the removed kidneys or disease in the contralateral kidney in 4.

It has also been suggested that there is a correlation between specific renal lesions and the subsequent response to nephrectomy but we were not able to observe this (Kincaid-Smith, 1961; Hunt *et al.*, 1970). The association between renal tumours and hypertension has been recognised for many years. The hypertensive effect is usually attributed to either ischaemia from compression of renal vessels or high cardiac output from arteriovenous shunts within the tumour. The probability that one of the tumours in this series secreted a pressor substance has been discussed elsewhere (Chisholm and Roy, 1971).

Even when nephrectomy fails immediately or subsequently to control hypertension, it has been noted by others that it may be easier to treat these patients because their anti-hypertensive drug requirement is considerably reduced; this was so in half of our failed cases.

Cerebro-vascular accidents are responsible for a significant number of deaths in hypertensive patients treated by hypotensive drugs (Hood *et al.*, 1963; Pickering, 1968, 1971; Breckenridge *et al.*, 1970) and similar fatalities can presumably complicate successful nephrectomy in such cases. However they were conspicuously absent in our successful nephrectomy patients. In contrast, subsequent myocardial infarction accounted for more than half the deaths in the present series despite control of hypertension by nephrectomy so that successful surgery is not an insurance against the risk of myocardial infarction in hypertensive patients.

Summary

A group of 47 patients with hypertension were followed for up to 16 years after unilateral nephrectomy.

The principal indication for the nephrectomy was hypertension in the presence of unilateral renal disease.

Methods of investigation and the pathological lesions are described.

60% of those patients followed for 7 years have maintained normal blood pressures without drug therapy. All of the patients with normal heart size and no hypertensive changes in the remaining kidney, remained normotensive for 5 years; for these reasons the prognosis was better in those under 40 years of age.

Where nephrectomy failed to lower the blood pressure the requirements for hypotensive therapy were considerably reduced.

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Reassessment of Divided Renal Function Study in Prediction of Surgical Results in Renovascular Hypertension

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It is generally accepted that divided renal function studies provide an accurate assessment of any improvement which might be gained by surgical correction of unilateral renal artery stenosis (Rapoport, 1960; Stamey, 1963; Howard and Connor, 1964; Foster *et al.*, 1969; Howard, 1969). On reviewing the literature (Fournier *et al.*, 1971), it is apparent that the prognostic value of this investigation is not very reliable, irrespective of which renal functional parameter is used. This is due in part to the fact that from 46% to 73% of patients with hypertension and renal artery stenosis are improved by surgery without significant unilateral changes in renal function having been found. Moreover there are 20% of patients whose hypertension is not improved but in whom "ischaemic" renal functional changes have been demonstrated. In order to decrease these false positive results Stamey (1965) suggested that surgical correction be performed only when the PAH clearance of the contralateral kidney is greater or equal to 200 ml/minute. However, Maxwell, Lupu and Franklin (1968); Foster *et al.* (1969) and Shapiro *et al.* (1969) have questioned the value of this additional information.

The persisting controversy as regards the prognostic value of divided renal function is possible due to the fact that most of the classical data has been determined on very small groups of patients and that comparison has been made between differing clinical groups. We therefore attempted to assess the prognostic value of divided renal function in a group of 33 patients who have been operated upon for renovascular hypertension. It was our aim:

- (i) To compare within the same group of patients the prognostic value of the classical ischaemic criteria.
- (ii) To determine a new ischaemic criterion with a higher prognostic value.
- (iii) To evaluate the prognostic value of measuring the PAH clearance of the contralateral kidney.

Materials and Methods

Data referring to 33 hypertensive patients who had undergone surgery for renovascular hypertension and who had previously had divided renal function tests were reviewed. In each case the diastolic blood pressure was above 95 mm Hg. There were 12 women and 21 men in the group. Preoperative evaluation included fundus examination, ECG, creatinine clearance, I.V.P. and renal arteriography. There was no evidence of gross renal functional impairment as all had a creatinine clearance above 60 ml/minute/1.73 m². The stenosis was unilateral and located on the main artery in 29 cases; it was bilateral in 3 cases and in 1 case the stenosis was located on a branch artery.

The surgical treatment consisted of nephrectomy in 4 cases and a re-vascularisation procedure

in 29 cases. The residual transtenotic gradient was always less than 30 mm Hg. Postoperative assessment has been evaluated according to the following criteria:

- (i) We have considered the patient "cured" if after 1 year the systolic pressure was below 140 mm Hg and the diastolic pressure below 90 mm Hg without treatment (Smith, 1956).
- (ii) We considered the patient "improved" if without treatment his systolic pressure decreased more than 50 mm Hg and his diastolic remained below 110 mm Hg: or when his blood pressure was kept within normal limits with thiazides only.
- (iii) If the preceding criteria were not satisfied the patient was considered "unimproved".

When hypertension failed to improve after surgery a minute sequence I.V.P. was performed in order to exclude graft thrombosis. On this assessment 11 patients were cured, 12 improved and 10 received no benefit from the surgical intervention.

Urine Separation Technique

Details of this technique have been previously published (Safar *et al.*, 1970). The patients received a normal diet of 120 mEq sodium per day and no diuretic or hypotensive treatment was given for a week prior to the test. Urine separation was obtained by bilateral ureteral catheterisation with a catheter in the bladder to collect urine bypassing the ureteric catheters. A diuresis was maintained using intravenous dextrose infusion without the addition of urea or ADH. Urine collections were started when the urine flow was steady above 3 ml/minute. The urine flow rate and urinary sodium and creatinine were estimated on 3 10-minute collections. In 22 cases separated PAH clearances were performed. For this purpose PAH was infused at a constant rate, after the priming dose had been given. Urine collections were performed after 45 minutes of PAH infusion. In 3 cases leakage round the ureteric catheters prevented accurate interpretation of urine flow rate and measurement of separated PAH clearances.

Expression of Results

For each patient, the following values were calculated from the measurements:

- (a) Δ Ucr % (difference of urinary concentration of creatinine). Two methods were used:

- (i) *Guedon's Method* (Guedon, Bourthoumieux and Lorente, 1965)

$$\Delta \text{Ucr \%} = \frac{\text{Ucr diseased side} - \text{Ucr non-diseased side}}{\text{Ucr non-diseased side}} \times 100$$

- (ii) *Howard's Method* (Howard and Connor, 1964)

$$\Delta \text{Ucr \%} = \frac{\text{Ucr diseased side} - \text{Ucr non-diseased side}}{\text{Ucr diseased side}} \times 100$$

The relation between the value obtained with Guedon's method (G) and that obtained with Howard's method (H) is:

$$G = \frac{100 H}{100 - H}$$

- (b) Δ V % (difference in urine flow rate) =

$$\frac{\text{V diseased side} - \text{V non-diseased side}}{\text{V non-diseased side}}$$

- (c) Δ UNa % (difference in urinary concentration of sodium) =

$$\frac{\text{UNa diseased side} - \text{UNa non-diseased side}}{\text{UNa non-diseased side}}$$

- (d) Rapoport's index (1960)

$$\frac{\text{UNa diseased side}}{\text{Ucr diseased side}} \times \frac{\text{Ucr non-diseased side}}{\text{UNa non-diseased side}}$$

The individual results are recorded in Table I.

Table I
Individual Results of Split Renal Function Studies

Name Age Sex (1) (2)	Location of Stenosis (3)	Δ Ucr %		Δ V % (4)	Δ UNa % (4)	UNa d. Ucr d. $\times$ Ucr n. UNa n. (4)	Contra- Lateral CPAH	Surgical Results
		Guedon (4)	Howard (4)					
1 AS 40 F	U	185	65	-73	-70	0.07	259	Cured
2 PIC 42 M	U	92	48	-75	-76	0.12	270	
3 MAL 35 F	U	82	45	-73	-9	0.50	387	
4 GAU 48 M	U	55	35	-62	-20	0.50	333	
5 HAM 23 F	U	36	26	-8	-8	0.66	308	
6 MEV 35 F	U	81	45	-43	-9	0.50	123	
7 ZAS 42 F	U	57	36	-40	-11	0.56	170	
8 FRE 43 M	U	82	45	-50	-71	0.13	164	
9 MAH 45 M	U	106	51	-46	-71	0.13	280	
10 LEB 51 F	U	400	72				162	
11 GRU 41 M	S	41	29	-77	-8	0.64		
12 LEM 38 F	U	300	76	-82	-82	0.42	263	Improved
13 NEV 36 F	U	1200	92	-81	-7	0.07	340	
14 TEY 38 M	U	527	84	-74	-40	0.09	250	
15 NEU 54 M	U	233	70	-90	-28	0.21	243	
16 REN 33 M	U	37	24	-33	-14	0.67	195	
17 VAL 25 F	U	60	37	-77	-77	0.65		
18 CON 46 M	U	134	58	-88	-2	0.41		
19 DUT 36 M	U	45	31	-20	-8	0.62		
20 DRI 33 M	U	74	42	-69	-32	0.38		
21 DAN 63 M	B	500	83	-23	-11	0.146		
22 MEN 49 M	B	21	17	-69	-32	0.38		
23 AIV 18 F	B	100	50	-55	-42	0.23		
24 BR 41 M	U	-25	-33	93	-14	1.13	310	Unimproved
25 CAM 52 M	U	0	0	0	18	1.18	198	
26 VAL 40 M	U	-11	-13	0	-6	1.04	200	
27 DER 47 F	U	-14	-17	3	3	1.2	206	
28 TES 42 M	U	700	87	-88	-2	0.12	117	
29 PL 42 M	U	-6	-6.5	-61	-2	1	445	
30 PER 20 F	U	29	22	-41	16	0.89	213	
31 MAL 52 M	U	38	28	0	-36	0.46		
33 POV 48 M	U	-3	-3.4	60				
32 PRI 56 M	U	-3	-3.7	-3	-16	0.86		

(1) Age at surgery.

(2) Sex: F = female, M = male.

(3) U = Unilateral of the main artery, S = segmental, B = Bilateral.

(4) See text.

Classical Ischaemic Criteria

(a) *Howard and Connor* (1964). For a stenosis of the main renal artery, ischaemia is considered to exist when the following criteria are satisfied: $\Delta V \leq -60\%$, $\Delta UNa \leq -15\%$ and $Ucr \geq +50\%$ with Howard's method of calculation, (i.e. 100% with Guedon's method).

For a stenosis of a branch artery: $\Delta V \leq -30\%$ and $\Delta Ucr \geq +20\%$ (or 25% with Guedon's method).

(b) *Howard* (1969). Ischaemia is considered to exist when there is a decrease in urine flow $\geq 20\%$ and an increase in urinary creatinine $\geq 20\%$ (i.e. 25% with Guedon's method).

- (c) *Rapoport* (1960). Ischaemia is present on the diseased side when the index is ≤ 0.6 .
- (d) *Guedon, Bourthoumleux and Lorente* (1965). Ischaemia is present when:
 - (i) $\Delta V \leq -50\%$, and
 - (ii) $\Delta \text{Ucr} \geq 30\%$
- (e) The ischaemic criteria proposed by *Stamey* (1963) and *Maxwell et al.* (1968) were not assessed in this study, since no urea nor ADH were given to our patients.

Principles of Study and Statistical Methods

(a) *Comparison of the prognostic value of the classical ischaemic criteria.* Initially the data of each patient were checked to see whether or not each of the above criteria was satisfied, and a prognostic assessment was made. For this purpose we calculated the number of improvements and non-improvements after surgery irrespective of any of the above criteria being satisfied. χ^2 of this distribution was then calculated. When it was above 3.84 it was considered that the criterion was significantly associated with surgical results (at $P \leq 0.05$) and that, therefore, it had a prognostic value. In this prognostic classification we called—"false positive", the cases in which the criterion was satisfied but surgery did not improve the hypertension, and "false negative" the cases in which the criterion was not satisfied but surgery did improve hypertension:

In addition the percentage of those cases with clinical improvement when the criterion was satisfied and the percentage when the criterion was not met was also calculated.

(b) *Determination of an ischaemic criterion of higher prognostic value.* For each parameter of kidney function disparity (V, UNa, Ucr) the following calculations were performed:

- (i) The group of the improved was first compared to the group of the unimproved using the sum rank test of Wilcoxon (*Geigy Scientific Tables*, 1963), which is the only applicable statistical method because distribution of the values was not gaussian.
- (ii) Individual values of these parameters were plotted for each of the 2 groups: the improved and the unimproved. A threshold value was chosen in order to give the best prognostic classification, as assessed with χ^2 test.
- (c) *Prognostic evaluation of contralateral PAH clearance in patients with unilateral functional stenosis.* This could be evaluated in 18 patients with unilateral functional stenosis (i.e. with an increase in urinary creatinine equal to or greater than 20%).

The number of false positive and false negative results were then calculated:

- (i) when only functional significance of the stenosis was required and
- (ii) when, furthermore, a contralateral PAH clearance equal to or greater than 200 ml/minute/1.73 m² was required.

Results

1. Comparison of the Classical Ischaemic Criteria

Table II shows the prognostic classification for each classical criterion:

- (a) Howard and Connor's criterion (1964) is characterised by no false positive results but a large number of false negative results so that the criterion has no prognostic value (χ^2 not significant).
- (b) Rapoport's index is more sensitive: chances of error are only 36% when the criterion is not satisfied and 10% when the criterion is satisfied. χ^2 test shows that it has a prognostic value ($P < 0.01$).
- (c) Guedon's criterion gives similar results: the chances of error are 36% when it is absent and 7% when it is present. The prognostic value of this criterion is high ($P < 0.01$).
- (d) Howard's (1969) criterion gives better results with a much higher χ^2 ($P < 0.0005$). The chances of error are small whether the criterion is satisfied (9%) or not satisfied (11%).

2. Determination of an Ischaemic Criterion of Higher Prognostic Value

(d) Prognostic Value of the Decrease in Urinary Sodium

Figure 1, A shows distribution of the differences in urinary sodium according to surgical results. The mean of the improved group (-31%) is significantly lower than the mean of the unimproved group (-4%).

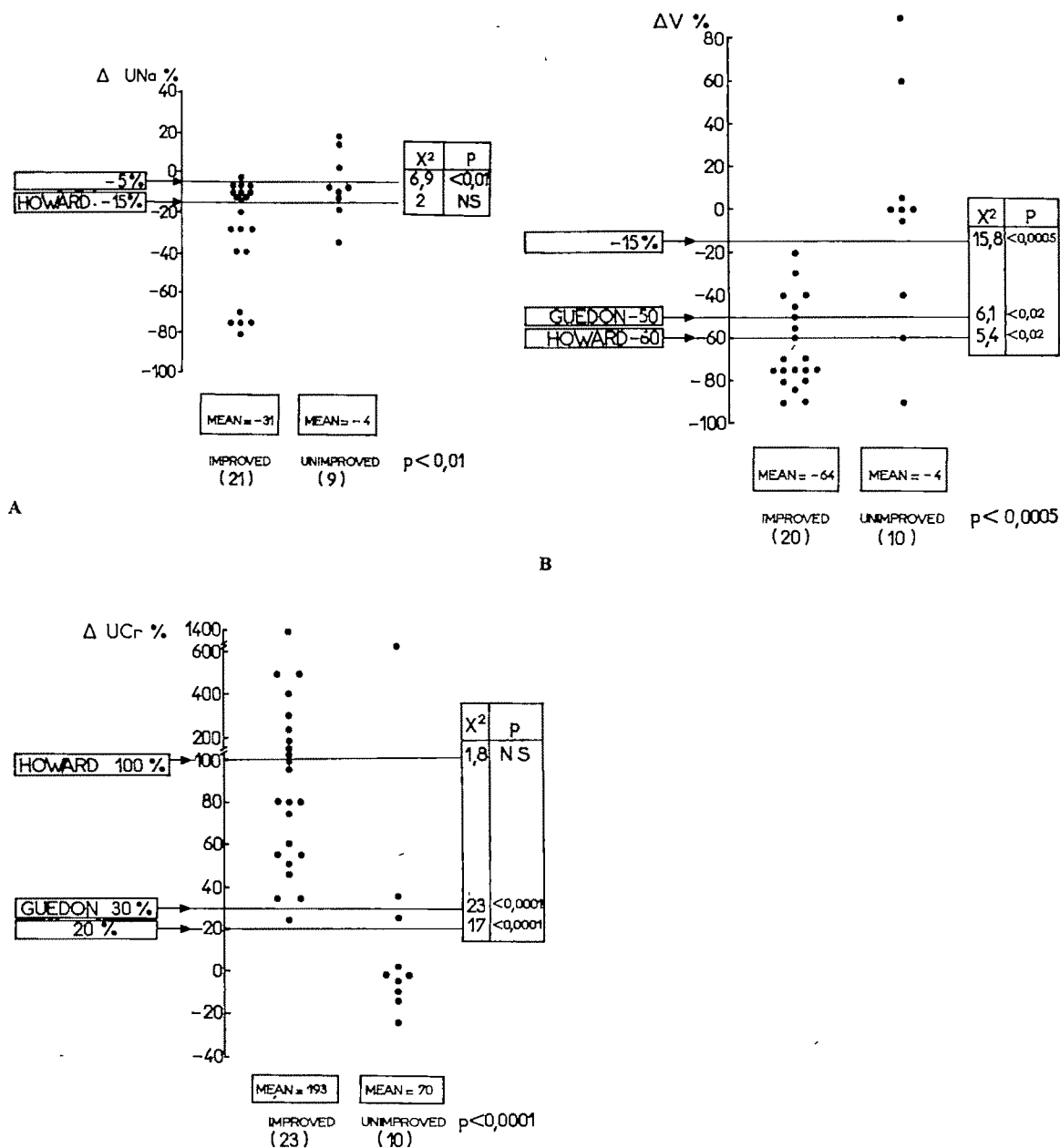


Fig. 1. A, Difference in urinary concentrations of sodium (Δ UNa %) and surgical results. B, Difference in urine flow rate (Δ V %) and surgical results. C, Difference in urinary concentrations of creatinine (Δ UCr %) and surgical results.

The threshold value of -15% as proposed by Howard and Connor (1964) obviously has no prognostic value because improvement occurs in 41% of the cases when this criterion is not satisfied.

(b) *Prognostic Value of the Decrease in Urine Flow* (Fig. 1, B)

The decrease in urine flow is significantly ($P < 0.01$) greater in the improved group (mean -64%) than in the unimproved group (-0.0%).

The threshold value giving the best prognostic classification is -15% with a χ^2 of 15.8 ($P < 0.0005$), no false negative results and 13% of false positive results. The prognostic value of this threshold is much better than those proposed by Howard and Connor (1964) and Guedon *et al.* (1965). The threshold of 20% proposed by Howard (1969) has the disadvantage of one case improved by surgery.

Table II

Surgical Results compared with Preoperative Presence or Absence of "Ischaemic" Criterion

Ischaemic Criterion	Total Number Evaluated	Criterion Satisfied		Criterion not Satisfied		χ^2 (P)	Percentage of Error when	
		Improved	Non-improved	Improved	Non-improved		Criterion Satisfied	Criterion Nonsatisfied
Howard, 1964	28	5	0	14	9	2.5 (NS)	0	57
Rapoport	30	17	2	4	7	7.7 ($P < 0.05$)	10	36
Guedon	30	14	1	6	9	7.3 ($P < 0.01$)	7	40
Howard, 1969	30	19	2	1	8	14 ($P < 0.0005$)	9	11
$\Delta \text{UCr} \geq 30\%$	33	22	2	1	8	23 ($P < 0.0001$)	8	11
$\Delta \text{UCr} \geq 25\%$	33	22	3	1	7	13.4 ($P < 0.0005$)	12	12
$\Delta \text{UCr} \geq 20\%$	33	23	3	0	7	17 ($P < 0.0001$)	11	0
$\text{UCr} \geq 20\%$	29	19	3	0	7	18.2 ($P < 0.0001$)	13	0
$\left. \begin{array}{l} \text{UCr} \geq 20\% \\ + \\ \text{UNa} \leq -5\% \\ \text{UCr} \geq 20\% \\ + \\ \text{UNa} \leq -5\% \\ + \\ \text{V} \leq -15\% \end{array} \right\}$	29	18	1	1	9	21 ($P < 0.0001$)	5	10
$\left. \begin{array}{l} \text{UNa} \leq -5\% \\ + \\ \text{V} \leq -15\% \end{array} \right\}$	29	18	0	1	10	21 ($P < 0.0001$)	0	9

* Total number of cases evaluated varies from 28 to 33 because in 5 patients V and/or UNa have not been simultaneously for technical reasons.

(c) *Prognostic Value of the Increase in Urinary Creatinine* (Fig. 1, c and Table II)

The mean increase in urinary creatinine is significantly greater ($P < 0.01$) in the improved group ($+193\%$) than in the unimproved group ($+70\%$). The threshold value giving the greatest

χ^2 is 30% ($\chi^2 = 23$ with $P < 0.0001$). A threshold value of 20% allows exclusion of 1 false negative and gives a χ^2 only slightly lower ($\chi^2 = 11$) with almost the same statistical significance ($P < 0.0005$). These 2 threshold values have a much greater prognostic value than the threshold of 100% proposed by Howard and Connor (1964). The threshold of 25% (Howard, 1969) is much better but excludes one case improved by surgery.

(d) *Prognostic Value of Association of 2 or 3 Parameters* (Table II)

This was assessed for the 29 patients in whom the 3 parameters have been calculated simultaneously. An increase in urinary creatinine equal to or greater than 20% is the most sensitive ischaemic criterion since it gives no false negative results; it gives, however, 3 false positive results.

When a decrease in urinary sodium equal to or less than -5% is required simultaneously, 2 false positive results are excluded but a false negative result appears. Simultaneous requirement of an increase in urinary creatinine equal to or less than -5% and a decrease in urine flow equal to or less than 15% gives no false positive and only 1 false negative result.

Table III

Prognostic Value of Contralateral CPAH in Patients with a Functional Renal Artery Stenosis

Prognostic Criteria	Prognostic Classification			Total	Percentage of Correctly Classified
	False Positive	False Negative	Correctly Classified		
$\Delta \text{UCr} \geq 20\%$	2	0	16	18	88%
$\Delta \text{UCr} \geq 20\%$ + Contralateral CPAH 200 ml/mn	1	5	12	18	66%

3. Prognostic Value of Contralateral CPAH (Table III)

Surgical results in the 18 cases with increased urinary concentration of creatinine in which separated PAH clearance was simultaneously measured, were as follows: 16 improvements and 2 unimprovements (*i.e.* 2 false positives). When a contralateral PAH clearance equal to or greater than 200 ml/minute was present the surgical results were 10 improvements and 1 failure. When contralateral PAH clearance was less than 200 ml/minute there were 5 improvements and 1 failure. Thus, when a contralateral PAH clearance equal to or greater than 200 ml/minute is required, the number of correctly classified patients decreases from 16 to 12 because if 1 false positive is excluded 5 false negatives appear.

Discussion

1. Lack of Sensitivity of the Classical Ischaemic Criteria

Evaluation of the classical ischaemic criteria in our single group of patients is comparable to that produced by other centres (Fournier *et al.*, 1971). It demonstrates their lack of sensitivity since the hypertension improves following surgery in 36% to 57% of the cases in which the criteria are not satisfied. The criteria mentioned by Howard in his Harvey Lecture in 1969 have not been used previously and so their exact value is unknown up to our assessment. In our series the

latter criteria appear to be more valuable than those proposed by Howard in 1964 since the chances of error when they are not satisfied is 11 % instead of 57 %.

2. *Determination of the Ischaemic Criterion with the Highest Prognostic Value*

The classical criteria are of little prognostic value because the threshold values being used to determine the presence of functional disparity are set too high. When considered individually each parameter is significantly different in the 2 groups of improved and unimproved patients, because the significance of the difference is being assessed with the Wilcoxon's test which does not take into account any threshold value. It is, therefore, important to define new threshold values on the basis of the highest χ^2 .

As regards the increase in urinary creatinine the highest χ^2 was obtained with a threshold value of 30 %. A threshold of 20 % however, was preferred as it enabled false negative results to be eliminated and the high χ^2 found with the threshold of 30 % is due to the elimination of a false positive. With the false positive results it is not certain that they are due exclusively to inadequacy of the criteria used as non-improvement may be due to technical failure of the vascular repair, which may not be apparent on a rapid sequence I.V.P., or to other factors not related to renal ischaemia. The simultaneous requirement of an increase in the urinary creatinine above 20 % and a decrease in the urinary sodium of less than 5 % coupled with a decrease in urine flow of greater than 15 % gives an even higher χ^2 but with a false negative result. For this reason we recommend simply an increase in urinary creatinine above 20 % as the criterion to decide whether or not stenosis induces ischaemia. This threshold value is very near the threshold of 25 % proposed recently by Howard in 1969. Its choice is furthermore justified by the fact that it is higher than the highest disparity of Ucr between the 2 kidneys in patients with essential hypertension without renal failure. This disparity has been proved not to exceed 15 % by Guedon and his colleagues (1965).

This criterion also seems valuable to interpret separated renal function studies when the stenosis is on a branch artery since in our single case of this type of lesion increase in urinary creatinine was 41 %.

3. *Prognostic Value of Contralateral CPAH*

In opposition to Stamey's proposals (1965) our experience confirms that of Foster *et al.* (1969), Maxwell *et al.* (1968) and Shapiro *et al.* (1969): when a stenosis is functional in a patient without renal failure (creatinine clearance equal to or greater than 60 ml/minute) the additional requirement of a PAH clearance of the contralateral kidney of equal to or greater than 200 ml/minute/1.73 m², does not improve the prediction of surgical results. In fact, this additional criterion increases the number of false negative results more than it decreases the number of false positive results. The value of measurement of separated PAH clearance for prognosis is therefore questionable.

Summary

A retrospective analysis of 33 patients who had undergone nephrectomy or revascularisation procedures for renovascular hypertension was carried out in order to assess the value of divided renal function studies in the prediction of the results.

The classical ischaemic criteria of Howard, Rapoport, and Guedon were proved to be insufficiently sensitive since, when they were not satisfied, surgery nevertheless improved hypertension in 36 % to 60 % of cases.

Our present experience leads us to recommend a single criterion of ischaemia—an increase in urinary concentration of creatinine (Δ Cr) of 20 % or more on the diseased side (calculated by dividing the difference between the 2 kidneys by the concentration on the healthy side, not the

diseased side as done by Howard). This single criterion has an excellent prognostic value ($P < 0.0001$) with no false negative and only 11% false positive results.

In opposition to Stamey's proposals (1965), the additional requirement of a contralateral PAH clearance equal to or greater than 200 ml/minute does not increase, but decreases, the prognostic value of separated renal function studies.

If our criterion is employed divided renal function tests can be considerably simplified. Infusion of PAH, urea and ADH are not required and only the simplest laboratory analyses are necessary.

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Surgical Procedures on Patients in End-stage Renal Failure

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Patients in end-stage renal failure being maintained on intermittent haemodialysis may require elective or emergency surgical procedures. These pose problems of management not encountered in the standard surgical risk patient. During the last 5 years, 113 major operations were carried out on patients undergoing regular haemodialysis for renal failure in this Unit. This paper reports this experience.

Patients

87 patients with irreversible end-stage renal failure underwent 113 surgical procedures other than transplantation under general anaesthesia at the Johannesburg General Hospital. The period under review extends from January 1967 to May 1972. The mean age of the patients was 34 years (Range: 12 to 52 years). 44 were females and 43 were males.

Table I

Causes of Renal Failure

Glomerulonephritis	40
Analgesic nephropathy	18
Pyelonephritis	11
Polycystic disease	7
Hypoplastic and/or dysplastic kidneys	4
Hypertensive nephropathy	3
Familial nephritis	1
Tuberculous renal disease	2
Medullary sponge kidney	1

The primary causes of renal failure are listed in Table I, glomerulonephritis being the most common. This is similar to the findings of others. Analgesic nephropathy was the next commonest condition, unlike other series, but reflecting the high incidence of this disease seen in this Unit (Kingsley *et al.*, 1972).

Pre-operative Status and Management

All patients operated on had been maintained on haemodialysis for periods varying from 1 day to 330 days prior to their operation, with a mean duration of 40 days.

Information regarding the pre-operative haemodialysis was available for 105 operations. 55 underwent haemodialysis on a Kiil dialyser for 12 to 14 hours; 50 patients were dialysed on the twin-coil type for periods of 4 to 8 hours. Only 1 patient underwent peritoneal dialysis pre-operatively.

Table II shows the time-lapse between the end of dialysis and the operation. Initially dialysis was completed on the morning of the operation. Later the pre-operative dialysis was completed at least 18 hours before commencement of operation.

Table II

Time Lapse between the End of
Dialysis and Commencement
of Operation

Hours	Number
0-6	35
13-18	5
19-24	21
25-47	41
48+	3

The mean blood urea concentration immediately after the pre-operative dialysis was 50 mg/100 ml with a range from 11 to 146 mg/100 ml. The mean serum creatinine concentration was 4.3 mg/100 ml with a range from 1.6 to 9.4 mg/100 ml.

Two hours before commencement of the operation the serum potassium concentration was checked. If this was more than 6 mEq/l, the operation was postponed until the patient had undergone further dialysis. This was only necessary on 2 occasions. If the serum potassium concentration was more than 5 but less than 6 mEq/l, an ion-exchange resin (Resonium A) was given rectally and the operation carried out as planned.

The mean haemoglobin concentration of these patients was 7.7 g/100 ml (Range: 5 to 15.6 g/100 ml).

Operative Procedures

Table III lists the operations done. The anaesthetic problems in renal failure patients have been discussed (Le Vine and Virtue, 1964; Vetten, 1970; Slawson, 1972) and are not considered here.

The commonest procedure carried out was bilateral nephrectomy in preparation for renal transplantation. The method used, a synchronous bilateral nephrectomy, has been described previously (van Blerk and Lissos, 1972). In patients with large polycystic kidneys, each kidney was removed at separate procedures and a standard nephrectomy was done in patients with a solitary kidney.

Five patients with radiological evidence of duodenal ulceration underwent surgical treatment for their ulcers. This was done to forestall any complications which might result from the use of large doses of steroids in the post-transplant period. In 4 of these patients nephrectomy was done at the same time. One patient required an emergency operation for bleeding from a duodenal ulcer.

Parathyroidectomy was performed on 4 occasions for secondary hyperparathyroidism. Miscellaneous procedures made up the remaining operations.

Postoperative Management

Initially postoperative care was done in the general wards, but because of untoward experiences patients were subsequently nursed in a surgical intensive care unit for the first 24 to 48 post-

operative hours. Postoperative fluids were administered intravenously according to measured sensible and estimated insensible losses. This was modified where necessary, according to assessment of hydration as judged clinically by blood pressure, pulse, tissue turgor and central venous pressure (C.V.P.) measurements. Serum potassium concentrations were measured every 6 hours and electrocardiographic tracings were taken at similar intervals to monitor for the development of hyperkalaemia.

Postoperative haemodialysis was postponed for as long as possible after the operation (Table IV). This was to prevent any haemorrhagic problems at the operative site which would

Table III

Type of Operation

Nephrectomy	91
Bilateral	63
Unilateral	17
Transplant	11
Gastro-intestinal	8
Vagotomy and drainage	1
Vagotomy, drainage, splenectomy and bilateral nephrectomy	1
Vagotomy and gastrectomy	1
Vagotomy, drainage and bilateral nephrectomy	2
Vagotomy, drainage, splenectomy and transplant nephrectomy	1
Haemorrhoidectomy	1
Cholecystectomy	1
Parathyroidectomy	4
Miscellaneous	10
Submucous resection	1
Urethroplasty	1
Bone biopsy	1
Sequestrectomy	2
Laparotomy	3
Bilateral nephrectomy and splenectomy	2

Table IV

Day of Postoperative Dialysis

Day of operation (3 peritoneal dialysis)	10
First postoperative day	34
Second	50
Third	10

follow the use of heparin during dialysis. In 7 instances haemodialysis was required during the first 12 postoperative hours because of a persistent hyperkalaemia which could not be controlled by any other means. Where haemodialysis was required within the first 24 hours of the operation, this was done using regional heparinisation. Three patients underwent peritoneal dialysis post-operatively.

Postoperative Complications (see Table V)

Hyperkalaemia (serum potassium concentration equal to, or more than 6 mEq/l) occurred after 43 operations. In 1 case this resulted in death. This case is discussed in detail later. If the serum

potassium concentration was more than 5 mEq/l, Resonium A was given (15-30 g orally or by retention enema). If the serum concentration was 6 mEq/l or higher, then, in addition to an ion-exchange resin, 10 units soluble insulin and 50 ml. 50% glucose were administered intravenously. If electrocardiographic evidence of hyperkalaemia was present, the above measures were also carried out. In 7 cases where conservative means of controlling the hyperkalaemia were unsuccessful, early postoperative dialysis was resorted to.

23 patients developed clotted external arteriovenous shunts within 1 week of their operation. Seven of these patients had significant postoperative hypotensive episodes. Anaesthetists and nurses were requested not to place sphygmomanometer cuffs on the limb with the shunt. However, clotting of shunts often occurred.

Postoperative respiratory problems occurred in 20 cases. Five patients suffered from significant episodes of hypoventilation. All completed their immediate pre-operative dialysis less than 24 hours before commencement of their operation. Two of these required assisted ventilation.

Table V
Postoperative Complications

Hyperkalaemia	43
Shunt clotting	23
Respiratory	20
Hypoventilation	5
Basal atelectasis and bronchopneumonia	15
Blood pressure	17
Hypertension	3
Hypotension	14
Haemorrhagic	8
Wound oozing + retroperitoneal haematoma	1
Wound oozing	4
Wound haematomata	3
Infections	6
Wound	4
Peritonitis	1
Septicaemia	1
Deep vein thrombosis	1
Wound dehiscence	1

15 cases developed postoperative basal atelectasis or bronchopneumonia, or both. These complications were treated with antibiotics and vigorous physiotherapy.

Eight patients had complications associated with excessive bleeding. Two of these patients completed their haemodialysis within 6 hours of commencement of their operation and 2 within 24 hours of commencement of their operation. One patient oozed from his wound and developed a retroperitoneal haematoma; 4 had excessive wound oozing and 3 developed wound haematomata. The haematomata were aspirated with a wide-bore needle and the wound oozing stopped spontaneously.

Severe hypotension in the immediate postoperative period occurred in 14 patients. 13 of these responded to the intravenous administration of normal saline until the C.V.P. had risen to 8 cm of water. One patient did not respond to vigorous therapy; this case is discussed more fully later. Four of these patients completed their pre-operative haemodialysis within 6 hours of being operated on and 4 within 24 hours. Three of these patients were on anti-hypertensive therapy. This was usually discontinued 12 to 48 hours pre-operatively; however, this was not done in the patient whose postoperative hypotension did not respond to therapy.

Three patients developed severe hypertension. This was easily controlled by the parenteral administration of hydralazine.

Serious non-respiratory infections occurred in 6 patients. One patient developed peritonitis and one septicaemia. Both these cases responded to the administration of antibiotics. Wound abscesses in 4 patients were drained by the removal of 1 or 2 skin sutures.

One patient developed intestinal obstruction whilst on peritoneal dialysis. He was then haemodialysed and a laparotomy carried out. Postoperatively his wound dehiscence and this was re-sutured under local anaesthesia.

In only 1 patient did a deep vein thrombosis develop in the postoperative period.

Mortality

There were 4 deaths in this series, *i.e.* a mortality of 3.5% of operative procedures performed.

Death 1

A 27-year-old man underwent bilateral nephrectomy. Eight hours postoperatively his serum potassium concentration was 8.3 mEq/l, and he was found to have a pneumothorax, probably related to a rib biopsy done at the time of his operation. This patient returned to the general wards after his operation and vigilance was not exercised in observing his serum potassium concentrations. Cardiac arrest occurred and although he was resuscitated and biochemical correction achieved, he did not regain consciousness.

Death 2

A 35-year-old female underwent simultaneous bilateral nephrectomy. Six hours after termination of her operation she became hypotensive and shocked. All resuscitatory measures failed. Two major factors were operative in the cause of her hypotension. She was on large doses of anti-hypertensive agents prior to her operation and her pre-operative dialysis was completed on the morning of her operation. Permission to perform autopsy was refused and the precise cause of her hypotension could not be ascertained.

Death 3

A 37-year-old man with polycystic disease of the kidneys developed a heart block and cardiac arrest while he was being placed in the lateral position for nephrectomy. He was resuscitated but remained decerebrate and died 6 days later. The factors leading to the cardiac arrest are unknown.

Death 4

A 44-year-old man with polycystic disease and tuberculous peritonitis had a successful first nephrectomy. A second operation was performed while he was still critically ill in order to remove the second kidney which was thought to be grossly infected. He died 2 days postoperatively from inanition and sepsis.

Discussion

In this series of patients a mortality rate of 3.5% of operations carried out is comparable to that of other series (Hampers *et al.*, 1968). The 4 deaths reported here were each due to a different cause. Several factors are considered to be of significance in this outcome and more careful attention to these might have resulted in survival of these patients.

In death 1 closer postoperative monitoring of the serum potassium concentration would have resulted in early recognition of hyperkalaemia and the administration of appropriate treatment. In death 2 it is suspected that dehydration induced during dialysis to control hypertension may have been too vigorous. Better assessment of this and more cautious use of anti-hypertensive drugs might have prevented her demise. In the 3rd death the cause of cardiac arrest could not be established and in the 4th, surgery was done in a critically ill patient in the hope of controlling a severe infection. Thus 2 of the 4 patients who died might have survived with more meticulous management.

Pre-operative, as well as intra- and postoperative factors are considered to be of significance in the many complications seen. These complications were predominantly haemorrhage, hypotension, hyperkalaemia, clotting of shunts and various infections.

Complications occurred with the same frequency in patients operated on within or after

24 hours of their last pre-operative dialysis. However, hypoventilation occurred only in those dialysed within the 24 hours pre-operatively. Cholinesterase concentrations are lowered by haemodialysis (Vandam *et al.*, 1962; Hesse *et al.*, 1970) and these will return to their initial values after dialysis. Because of the possible association between early pre-operative dialysis and hypoventilation it would seem advisable not to do elective surgery within 24 hours of the last dialysis.

While a clear-cut relationship between other complications and the immediate pre-operative dialysis is not seen, it is likely that a multiplicity of factors, including the preceding dialysis, might have contributed to these.

Four patients who had haemorrhagic complications completed their immediate pre-operative haemodialysis within 24 hours of commencement of the operation. A delay following dialysis will allow the effect of the heparin used to be eliminated and thus prevent the bleeding complications of heparinisation during and following surgery. The use of regional heparinisation does not prevent this tendency to bleed as the "anti-coagulation rebound phenomenon" may occur following the use of regional heparinisation. (Hampers, Blaurox and Merrill, 1966). Uraemic patients show a tendency to bleed but this is reduced in well-dialysed patients (Nakamoto and Kolff, 1964). The mean pre-operative blood urea in this group was 50 mg per 100 ml and the mean serum creatinine trend was 4.3 mg per 100 ml, thus uraemia is not thought to be a major factor in causing the haemorrhages in this series. During the operation meticulous attention must be paid to haemostasis to prevent postoperative oozing.

Haemodynamic equilibrium is disturbed during dialysis, usually due to excessive fluid depletion and thus hypotension may follow if surgery is commenced too soon after dialysis. Seven of the patients developing hypotensive episodes were dialysed within 24 hours of commencement of their operation.

In addition nephrectomy will, in some patients, remove a stimulus to vasoconstriction and patients undergoing this operation may become hypotensive (Lazarus *et al.*, 1972). This will be particularly evident in those patients requiring anti-hypertensive treatment while on dialysis, but may also be seen in patients whose hypertension is controlled by dialysis. Ideally, a C.V.P. catheter should be inserted at least 4 hours pre-operatively and the C.V.P. level should be maintained at 8 cm of water, pre-, intra- and post-operatively. This simple expedient will help in preventing hypotensive complications.

Postoperative chest infections occurred in a significant number of patients. Patients should have vigorous pre- and post-operative physiotherapy to prevent this complication. In addition, sterile endotracheal tubes must be used to avoid bacterial contamination of the respiratory tract. Infections at other sites were all controlled by treatment. However, 1 patient had a flare-up of her dormant and apparently controlled wound infection when she was placed on immuno-suppressive therapy following her subsequent renal transplant. This infection was ultimately responsible for her death. It is therefore of the utmost importance to prevent infections in patients who will eventually undergo renal transplantation.

Hyperkalaemia was the commonest postoperative complication. This is due in part to the hyper-catabolic state following a surgical procedure. In a study of anaesthesia in renal failure patients, Goggin and Joekes (1971) postulated that the respiratory compensation of the conscious patient might be abolished by anaesthesia. The resulting sudden increase in PaCO_2 with a fall in arterial pH may cause an increase in plasma potassium concentration. If blood transfusion should be required, fresh blood must be used to minimise the danger of potassium infusion. Extreme vigilance must be exercised in the postoperative period to detect an early rise in the serum potassium concentrations. Both serum potassium estimation and electrocardiographic monitoring must be carried out at regular and frequent intervals.

It has been reported that renal failure may be responsible for poor wound healing (Schreiner and Maher, 1963; Nayman, 1966), and anaemia, too, has been implicated. In this series, in only 1 patient did the wound dehiscence and he was markedly debilitated. If patients are adequately dialysed, wound healing will not present any problems.

Traditionally a low haemoglobin concentration is a contra-indication to surgery (Lunn and Elwood, 1970). In this series the mean pre-operative haemoglobin concentration was 7.7 g/100 ml and this low concentration did not appear to be associated with any complications. In fact, patients tolerated the procedures well.

Post-operative clotting of external arteriovenous shunts occurred frequently. Dehydration and hypotension with reduction in the rate of blood flow through the shunt may have accounted for some of these cases. In addition, the known effect of any surgical procedure on blood coagulability and unrecognised factors such as position of the cannulated limb in the intra- and post-operative period and the placing of sphygmomanometer cuffs may have contributed.

Summary

113 major surgical procedures were carried out on 87 patients with irreversible renal failure and being maintained on haemodialysis.

The commonest postoperative complication was hyperkalaemia (43), followed by shunt clotting (23), respiratory complications (20), hypotension (14), hypertension (3), haemorrhage (8), infections (6), deep vein thrombosis (1) and wound dehiscence (1).

The operative mortality was 3.5%.

The time of pre-operative dialysis appears to have a relationship to the postoperative complications.

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Simple Renal Cyst in a Newborn

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Although large simple cysts of the kidney are common findings in adult life, the literature reports few references to this type of lesion in infants and children.

The presenting clinical feature of a simple renal cyst is a silent abdominal mass and normal urinary findings.

With conventional radiological procedures the differentiation from renal neoplasm may be difficult. Renal arteriography could differentiate tumours from simple renal cysts but the incidence is so overwhelmingly in favour of tumours in the under-5-year age group that serious objections could be raised against arteriography or venacavography as a routine diagnostic procedure.

It is accepted that the existence of an abdominal mass in an infant is so suggestive of neoplasm that surgical exploration becomes obligatory. When a cyst is found on exploration, uncapping of the cyst is the procedure of choice and only in the face of complete destruction of the renal parenchyma is nephrectomy indicated.

Case Report. Following a normal pregnancy and delivery, F. S., a 10-day-old male was referred to our department during November 1969. The referring sign was dribbling when passing urine.

On admission we found a newborn weighing 3,900 g in good general condition. Clinical examination showed a huge mass filling the entire left side of the abdomen, a palpable urinary bladder and bilateral inguinal hernias. There were no other abnormal physical findings. Laboratory investigations, which included urinalysis and blood chemistry, were within normal limits. The excretory pyelogram (Fig. 1A) showed the left kidney to be displaced to the right side and both ureters were elongated, tortuous and dilated. Voiding urethrocytography (Fig. 1B) showed the presence of a posterior urethral valve but there was no vesico-ureteral reflux. The elevated transverse colon and the anterior displacement of the descending colon in the lateral barium enema films confirmed the presence of a retroperitoneal mass (Fig. 1C).

On 23rd November 1969, the child was operated upon under general anaesthesia. The retroperitoneal region was approached through a paramedian incision. A large unilocular cyst of the left kidney was found which was pushing the kidney to the right. The cyst was uncapped and excised after 450 ml of serous fluid had been aspirated. The renal parenchyma was found to be normal macroscopically.

Histology showed the cyst to be composed of fibrous tissue lined by a single layer of cuboidal epithelium.

The bladder was drained by means of an in-dwelling catheter No. 10 F. When the catheter was removed 10 days later the urine stream was satisfactory and there was no residual urine in the bladder. The infant was discharged 18 days following the operation after an uneventful recovery.

Six weeks later the infant was re-admitted to our department for further urological investigations. On admission he was in good general condition and weighed 5,300 g. Physical examination revealed a still palpable bladder. Klebsiella infection of the urine was found but otherwise all laboratory findings were normal. An excretory pyelogram (Fig. 2A) now showed bilateral uretero-hydronephrosis and that the left kidney had commenced its return to its normal anatomical position. The voiding urethro-cystogram (Fig. 2B) again showed the posterior urethral valve and the new finding of severe vesico-ureteric reflux on the right but not on the left (the side of the excised cyst).

The infant's bladder was again drained by a catheter in order to dilate the urethra to F.12 and a transurethral resection of the valve was performed.

The baby was completely well for 4 months after this last operation but then difficulties in micturition recurred. On cysto-urethroscopy a small remnant of the valve was found. This was removed by transurethral resection.

The child is now over 2 years of age and under periodic observation. He is in good health and symptomless as far as the urinary tract is concerned. His urine is sterile and his renal function tests are normal. The latest radiological study in April 1972, which comprised excretory pyelography and voiding urethrocytography, showed bilateral normally positioned kidneys with moderate dilatation of their collecting systems. The bladder outlet and the urethra were normal (Figs. 3A and B).

Comment

We justify the report of this case on account of its unusual nature when compared with the small group of simple renal cysts in infants and children so far reported in the literature.

DeWeerd and Simon (1956) reviewed the literature in 1956 and collected 21 cases of simple

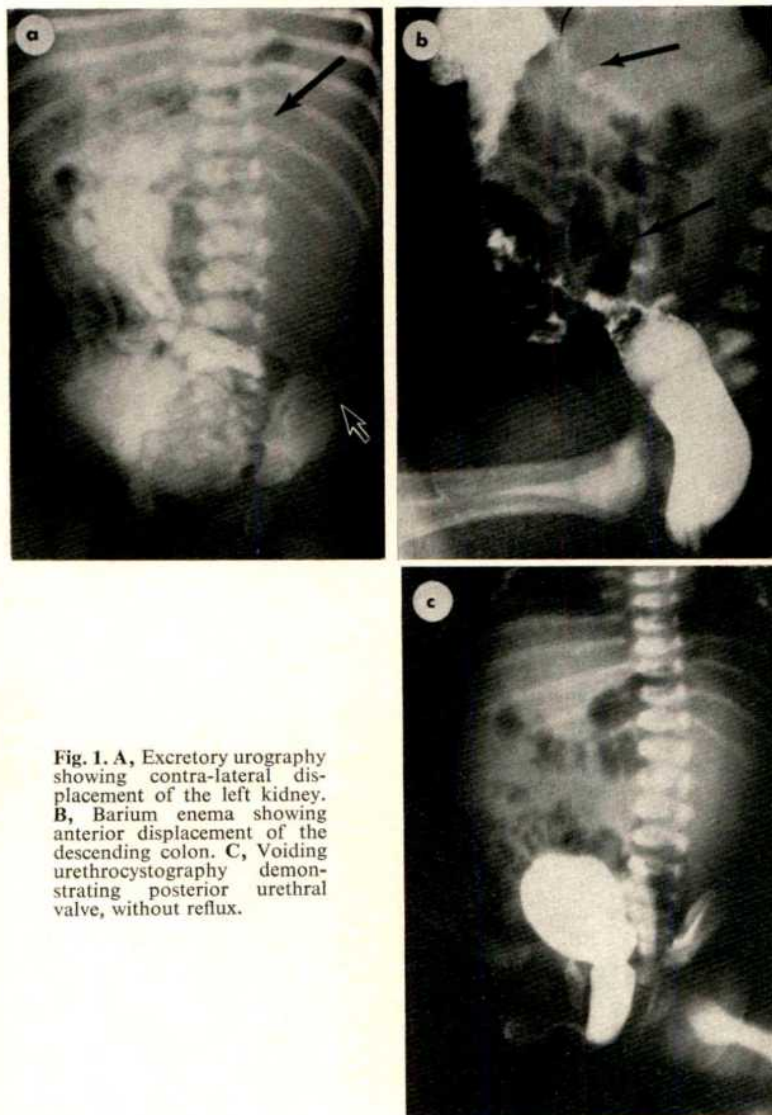


Fig. 1. A, Excretory urography showing contra-lateral displacement of the left kidney. **B,** Barium enema showing anterior displacement of the descending colon. **C,** Voiding urethrocytography demonstrating posterior urethral valve, without reflux.

cysts in infants and children, of which 5 were their own cases. Among these cases only 1 was a newborn and the cyst was not found until autopsy. The only 2 reports of simple cysts of the kidney diagnosed and treated in the newborn (of ages 4 and 6 weeks) were reported by Travers (1954) and Ahmed (1972).

Our review of the literature revealed only 4 reports of simple cysts in children in addition to those reported by DeWeerd and Travers. These are reports by Gall and Kurtz (1958), Melicow

and Uson (1959), Ahmed (1972) and Gosalbez, and none was in a newborn. In a study of the literature we were unable to find a case with the particular features we have reported, namely,

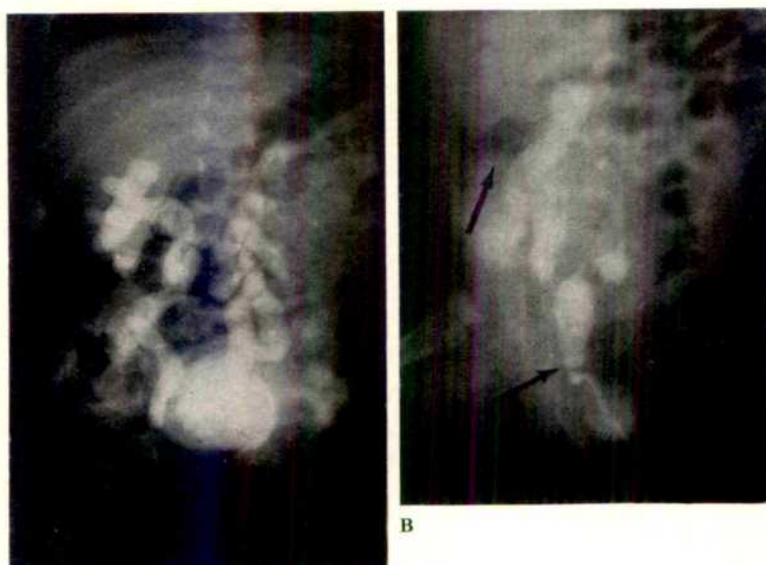


Fig. 2. A, Excretory urography showing bilateral uretero-hydronephrosis. The left kidney is returning to its normal position. B, Voiding urethrocystography showing posterior urethral valve with right vesico-ureteric reflux.

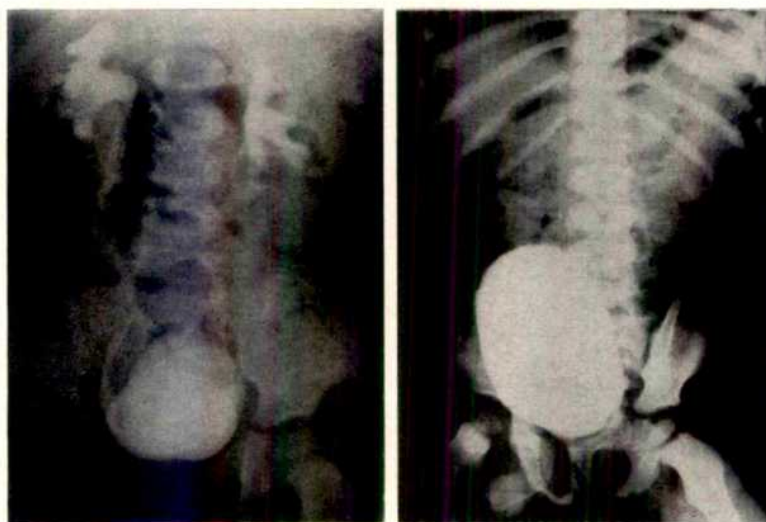


Fig. 3. A, Excretory urography showing significant improvement of the hydronephrosis and a normal position of the left kidney. B, Voiding urethrocystography showing normal bladder outlet and urethra, without reflux.

contralateral displacement of the kidney by a cyst followed by a rapid return of the organ to its normal position following operation.

The appearance of reflux after the removal of the cyst in our case makes one speculate that the high hydrostatic pressure in the cyst (Bjerle, Lindqvist and Michaelson, 1971) might have prevented vesico-ureteric reflux during intra-uterine life.

Summary

A case of a large simple renal cyst in a newborn with posterior urethral valves is presented.

The affected left kidney was contralaterally displaced and returned to its normal position after operation.

Reflux up the contralateral ureter appeared after removal of the cyst.

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Carcinoma of the Renal Pelvis: a Review of 43 cases

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In a prospective study of patients with transitional cell carcinoma of the ureter we found that the survival was directly related to the histological grading of the tumours, and a poor prognosis was indicated by invasion of the muscle coat and also enlargement or non-function of the affected kidney (Williams and Mitchell, 1973). Similar observations have also been described for patients with transitional cell carcinoma of the renal pelvis. Although there is no universally accepted method of grading these tumours, prognosis is probably related inversely to the degree of histological differentiation of the tumour (Grace *et al.*, 1967; Grabstald, Whitmore and Melamed, 1971), and a poor prognosis is found when the tumour has infiltrated extrarenally or into the renal substance (McDonald and Priestley, 1944). Higgins (1953) noted that the 13 of his 47 patients with a palpable kidney on the affected side had a grave prognosis, but this figure included 5 patients with squamous cell carcinoma, which is recognised to have an extremely poor outlook regardless of the choice of treatment (Dees, 1956).

With carcinoma of the ureter it has been shown that non-function of the kidney suggests a poor prognosis (Tresidder and Warren, 1954; Williams and Mitchell, 1973), and this is probably the result of early complete obstruction of the ureter producing hydronephrosis and impairment of renal function. Becker (1969) described 5 patients with transitional cell carcinoma of the renal pelvis and non-functioning kidney and showed that they fared particularly badly. However, histological examination of these patients' kidneys showed no evidence of either ureteric obstruction or renal vein involvement, but there was extensive invasion with areas of fibrotic reaction within the kidney, which then had insufficient healthy tissue to produce radiological function. This he compared with renal cell carcinoma, where the finding of non-function is believed to indicate renal vein obstruction by invading tumour (Lalli, 1966).

In this prospective study of 43 patients with transitional cell carcinoma of the renal pelvis we consider the factors that may influence prognosis.

Patients

All the cases of transitional cell carcinoma of the renal pelvis referred to the United Bristol Hospitals and Southmead General Hospital during the 20-year period 1951 to 1970 have been included in this study. All the diagnoses were confirmed by histological examination and the tumours graded into 3 histological grades in accordance with the method adopted by the Bristol Bladder Tumour Registry (Miller, Mitchell and Brown, 1969).

1. **Low Grade Tumours** are more than 5 cells thick, with regular basement cells, showing a palisade arrangement and some variations in size and shape of cells and nuclei.

2. **Average Grade Tumours** are more than 5 cells thick, with basement cells irregular in size and shape and nuclei tending to be circular. The cells are similar in all layers with little differentiation, but some variations in the shape and depth of staining of the nuclei are present.

3. **High Grade Tumours** are just identifiable as transitional cell epithelium with no differentiation into layers. Basement cells are not identifiable and there is a great variation in size and shape of the cells and nuclei. Tumour giant cells are frequently seen and many darkly staining nuclei are present.

Findings

During the 20-year period there were 43 cases of carcinoma of the renal pelvis and 2,770 cases of carcinoma of the bladder recorded by the Bristol Bladder Tumour Registry. This gives an approximate ratio of 1 case of carcinoma of the renal pelvis for every 64 cases of carcinoma of the bladder.

During the same period, there were 54 cases of ureteric tumour, 34 presenting as primary neoplasms of ureter, the remainder showing neoplasia of other parts of the urothelial tract as well as the ureter, though the latter was probably the site of the original tumour (Williams and Mitchell, 1973). Of the 43 patients with carcinoma of the renal pelvis, 12 presented during the period 1951 to 1960 and 31 during the years 1961 to 1970. 22 lesions were in the right kidney and 21 in the left.

20 patients had low grade tumours (average age 60 years), 15 average grade (average age 61 years) and 8 high grade tumours (average age 60 years). The ages ranged from 31 to 76 years. 33 patients were male and 10 female and no significant difference in this ratio of 3 : 1 was found between the 3 grades.

Presenting Symptoms

36 patients presented with haematuria. Of the remaining 7 patients, 3 complained of loin pain, 2 were discovered at intravenous pyelography performed for symptoms of prostatism, 1 during the investigation of enuresis and 1 patient with a solitary kidney was admitted with anuria. The average period of haematuria before presentation was 7 months, but this figure is distorted by the inclusion of 1 patient, who endured his haematuria for 8 years before seeking advice. If he is excluded, the average period of haematuria was 4.5 months and no difference was found between the 3 histological groups. 13 of these patients also complained of loin pain or backache and 2 were admitted because of clot retention of urine.

Signs

Seven patients had a palpable kidney on the affected side. Two of these patients had low grade tumours, 2 average grade and 3 high grade lesions.

Investigations

Urine

A mid stream specimen was collected from 40 patients, catheter specimens from 2 patients with clot retention, and 1 patient had anuria. 23 specimens contained red blood cells and a significant urinary infection was found in 6.

Excretion Urography (Table I)

Six patients did not have this examination. In 3 of these an emergency cystoscopy was carried out at the time of the haematuria, when blood was seen issuing from the ureteric orifice and retrograde pyelography was performed, confirming a diagnosis of carcinoma of the renal pelvis (see below). One patient had an emergency exploration for a pyonephrosis and 1 patient with anuria had an emergency nephrostomy carried out during which the diagnosis was made. The remaining patient died following a cerebral haemorrhage before his investigations had been completed.

From Table I it can be seen that for all patients the findings indicated pathology requiring an urgent diagnosis and in 28 cases a definite diagnosis of carcinoma was made by the radiologist. In 2 patients urinary calculi were also seen in the kidney, but they did not obscure the diagnosis.

Retrograde Pyelography

The earlier cases were investigated routinely by retrograde pyelography and in some later cases by retrograde ureterography using a Braash or a Chevassu bulb. Investigations were carried out

in 26 patients and after considering the results in conjunction with the findings of excretion urography, a convincing radiological diagnosis was obtained in all of the patients.

Table I
Results of Excretion Urography in 37 Patients

	Total	Grade		
		Low (17)	Average (14)	High (6)
(a) Space-occupying lesion	27	12	12	3
(b) Non-function	5	2	2	1
(c) Diminished function	5	3	0	2
Total with abnormal findings	37	17	14	6

Cystoscopy

Blood was seen issuing from the ureteric orifice of 7 patients and co-existing bladder tumours were found in 3 patients. Two of these 3 patients had a past history of bladder tumour for which they were being reviewed at regular intervals.

Delay in Treatment

The average period between presentation and treatment was 1.7 months. In no case was there undue delay in diagnosis and treatment.

Type of Treatment (Table II)

The policy for treatment of this condition during the period under study, was nephro-ureterectomy. This was performed for 40 patients, in 20 of whom the intramural ureter was removed with

Table II
Treatment Carried Out in the 43 Patients

	Total	Grade		
		Low	Average	High
(a) Nephro-ureterectomy removing a cuff of bladder	20	10	8	2
(b) Nephro-ureterectomy not taking a cuff of bladder	20	9	5	6
(c) Radiotherapy alone	1	0	1	0
(d) Nephrostomy	1	0	1	0
(e) Nil	1	1	0	0
Total	43	20	15	8

a cuff of bladder. Adequate removal of the intramural ureter can only be ensured by intravesical exposure of the ureteric orifice itself, which is purse-stringed and dissected through the bladder wall (Mitchell, 1969; Williams and Mitchell, 1973). One patient was treated with radiotherapy and 2 died before definitive treatment could be carried out.

Subsequent Development of Bladder Tumours (Table III)

Three patients had co-existing bladder tumours and 17 (16 male and 1 female) of the remaining 37 patients available for follow-up subsequently developed bladder carcinoma. These occurred with equal frequency in the 3 histological groups. Of 17 patients who had adequate excision of a

Table III

Subsequent Development of Bladder Carcinoma after Treatment for Carcinoma of the Renal Pelvis

	Total	Cuff of Bladder Removed	Inadequate Excision
Bladder neoplasia	17	5	12
No bladder neoplasia	20	12	8

Three patients are excluded because the bladder tumour was found at the same time as the carcinoma of the renal pelvis. All 3 patients subsequently developed further bladder tumours.

cuff of bladder, only 5 developed bladder tumours, but 12 of the 20 patients who had inadequate cuff excision, later developed bladder carcinoma. In 12 patients these tumours were in the region of the affected ureteric orifice or where it had been before nephro-ureterectomy. 13 of the bladder tumours were of the same histological grade as the original pelvic lesion. In 1 the grade was higher and in 3 the bladder tumours were of a lower grade.

The average period between the treatment of carcinoma of the renal pelvis and the development of bladder tumours, was 15 months and there was no significant difference in the ages of the patients who did and did not develop carcinoma of the bladder. These were 59 years and 61 years respectively.

Table IV

Survival of 43 Patients with Ureteric Tumours, compared with the Expected Survival for the General Population in that Age Group (*Registrar General's Statistical Review 1967*). For Convenience the Figures are Expressed as Percentages

A.	GRADE	Grade			Expected Survival	
		Low	Average	High		
	5 years	36	40	25	90	
	10 years	9	0	0	76	
B.	STAGE	Invasion Present		No Invasion Present		
	5 years	11		48		90
	10 years	0		6		76

Prognosis (Table IV)

The prognosis for all patients was poor in each of the histological grades, and once invasion of the renal substance or extrarenal tissues had occurred, the prognosis deteriorated markedly.

The 9 patients with invasive tumours (4 average grade and 5 high grade) were dead with evidence of distant metastases after an average period of 1 year 5 months.

Discussion

In 1956 O'Connor reviewed cases of transitional cell carcinoma of the ureter and renal pelvis collected from the world literature and concluded that there had been a marked increase in their incidence. In a previous paper we were able to confirm this finding for carcinoma of the ureter (Williams and Mitchell, 1973). O'Connor believed that this is a real increase and not the result of improved diagnostic procedures. However, we find it difficult to be so dogmatic as, during this period, there have been considerable advances in diagnostic techniques and an increase in the number of urological units which should now ensure that the diagnosis is rarely missed. In the present study of lesions in the renal pelvis, we find that more than two-thirds of our patients presented during the 1961 to 1970 decade.

Like carcinoma of the ureter, the condition is more common in males (Abeshouse, 1956) and our ratio of 3.3 males to each female is similar to that found in other series of any size (McDonald and Priestley, 1944; Riches, Griffiths and Thackray, 1951; Grabstald *et al.*, 1971). In certain series, the tumour has appeared to occur more frequently on one particular side. In some it is the right kidney (Taylor, 1959; Grace *et al.*, 1967; Grabstald *et al.*, 1971) and the left in others (McDonald and Priestley, 1944). These authors have tried to explain these differences, but when all these series are combined, no particular predilection to side was found. This was noted in our study, where both kidneys were equally affected.

Seven patients were found to have a palpable kidney on the affected side, and their clinical course did not differ from the remaining 36 patients. Higgins (1953) found that a palpable kidney indicated a bad prognosis for patients with carcinoma of the renal pelvis. Unfortunately, half of his cases with a palpable kidney had squamous cell tumours, and it is accepted that they fare worse than patients with transitional cell lesions (Dees, 1956). Of our 7 patients, 3 died from metastases after an average period of 8 months, 1 died of a pulmonary embolus after 1.5 years, and 3 are alive and well after intervals of 3 years, 4 years and 8 years.

In all cases where excretion urography, with or without retrograde pyelography, was carried out, a definite diagnosis was made. The commonest finding of a space-occupying lesion is similar to previous studies (Taylor, 1959; Grace *et al.*, 1967; Grabstald *et al.*, 1971). Becker (1969) claimed that non-visualisation of the kidney on excretion urography was the result of invasion of the renal substance by the tumour and indicated a poor prognosis. Four of our patients had non-function of the kidney. They included 2 patients with low grade tumours and no evidence of invasion of the renal substance. One is alive and well after 5.5 years and the other died of other causes after 3 years. There was no evidence of metastatic spread found at postmortem. The remaining 2 patients with average and high grade lesions died of metastases 1 year and 6 months after treatment respectively. With so few patients in this group, we feel that we can draw no conclusion about the finding of a functionless kidney.

It had been suggested that these tumours are associated with stones (MacLean and Fowler, 1956; Seth-Smith, 1959). In our series only 2 patients had co-existing urinary calculi, and we believe that this suggestion is the result of studying small numbers of cases which included patients with squamous cell tumours.

Like previous authors we found a high incidence of bladder carcinomata amongst our patients (McDonald and Priestley, 1944; Greene, Hayllar and Bogash, 1958; Grabstald *et al.*, 1971). Three of our patients had co-existing bladder lesions, and 17 of the remaining 40 patients developed bladder tumours at a later date. Grabstald *et al.* (1971) noted that bladder tumours developed within 3 years of treatment for the carcinoma of the renal pelvis, were more common in men than women, and occurred in somewhat younger patients. Our average time between treatment for the tumour in the renal pelvis and the development of bladder tumours was 15 months,

and in only 1 case was the interval longer than 3 years. The bias towards male patients was confirmed as 16 of 32 male patients developed bladder cancer compared with only 1 of 8 female patients. However, the average age for patients developing carcinoma of the bladder was 59 years compared with 61 years for those who did not, and there is no difference between these groups.

As with carcinoma of the ureter, there was an increased incidence of tumours developing in the bladder when nephroureterectomy was carried out without adequate removal of a cuff of bladder wall. In 12 of our 17 cases the bladder tumour was in the region of the affected ureteric orifice or where it had been before operation. This relationship of the bladder tumour to the involved ureteric orifice is well established (McDonald and Priestley, 1944; Greene *et al.*, 1958; Newman *et al.*; Grace *et al.*, 1967). These findings support the removal of a cuff of bladder with the nephroureterectomy as being the treatment of choice for this condition, as in primary carcinoma of the ureter. In fact, Taylor (1959) claimed from the results of his study that total removal of the ureter with a recurrence rate of 15.4% was much more satisfactory than incomplete removal of the ureter with a recurrence rate in the lower ureter or ureteric stump and bladder of 33%.

We found no relationship between the grade of tumour in the renal pelvis and the tendency to develop bladder carcinomata. This contrasts with the studies of McDonald and Priestley (1944) and Kaplan, McDonald and Thompson (1951) who found a higher incidence of bladder tumours with the lower grades of tumour in the renal pelvis.

The overall prognosis for the patients included in our series was poor, and there was no obvious relationship between the 5-year survival time and the histological grade of the tumour, though at 10 years there was a small bias in favour of the low grade tumour. Other authors claim an inverse relationship between the grade of the tumour and survival (Humphreys and Foot, 1960; Grace *et al.*, 1967; Grabstald *et al.*, 1971). However, on analysing their figures this relationship is not particularly striking, and the overall prognosis for their patients was similar to ours. Once infiltration into the kidney substance or extrarenal tissue had occurred, we found that there was a marked deterioration in the prognosis. This has also been demonstrated by McDonald and Priestley (1944) and Grabstald *et al.* (1971) who noted that the actual type of treatment did not influence the prognosis for these cases.

Summary

A prospective study of 43 cases of transitional cell carcinoma of the renal pelvis that presented over a 20-year period is reported.

The overall prognosis of these patients was poor and was not related to their histological grading. However, once invasion had occurred the prognosis deteriorated markedly.

A large proportion of the patients subsequently developed bladder carcinomata, and the risk was increased when the intramural portion of the ureter was not removed completely.

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Carcinoma of the Ureter—a Review of 54 Cases

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Because of the comparative rarity of transitional cell carcinoma of the ureter, knowledge of its behaviour pattern and its response to treatment has developed only from collective analyses of numerous small series of cases from the literature (Mortensen and Murphy, 1950; Abeshouse, 1956). The value of data collected in this way is limited by lack of adequate details regarding follow-up, variation in the methods of grading and different methods of treatment. Recently attempts have been made to overcome these problems by studying larger numbers of cases investigated and treated at a single centre (McIntyre, Pyrah and Raper, 1965; Hawtrey, 1971). The fact that larger numbers of cases are now available for study has led to the suggestion that carcinoma of the ureter is increasing in frequency (Bloom, Vidone and Lytton, 1970).

On the other hand, difficulty and delay in diagnosis has been admitted in nearly every paper on this subject and the apparent increase in the number of cases may be purely a demonstration of more accurate diagnosis. The undiagnosed cases in the past would probably have progressed to involve other parts of the urinary tract so that the exact site of origin of the transitional cell tumour in the ureter was no longer obvious at the time of postmortem. Similarly, the undifferentiated tumour might have spread locally into the surrounding structures, giving the impression of a retroperitoneal tumour. Those deaths in which no postmortem was carried out could have been assumed to have died of secondaries from the associated carcinoma of bladder or kidney.

In retrospect, the actual diagnosis of some of the earlier cases is open to doubt and even well-documented cases such as Davy's (1884), which is believed to be the first acceptable description of a ureteric tumour, may have been a carcinoma of the rectum invading the ureter, the tumour being so advanced at the time it was first recognised.

The histological grading of transitional cell tumours produces confusion as different criteria have been used by various authors, and this has complicated any accurate comparison between one series and another. Confusion has arisen between true benign papillomata and cancers of low-grade malignancy which, although appearing benign, are capable of infiltration or metastasis (Riches, 1964).

Another difficulty encountered when analysing different series, is that no distinction has been made between primary and possible secondary spread from a pre-existing bladder tumour. In the light of our present knowledge of the methods of spread of urothelial tumours, the inclusion of cases where a carcinoma of the bladder has been discovered either before or at the time of diagnosing the ureteric tumours (McIntyre, Pyrah and Raper, 1965; Hawtrey, 1971) makes it impossible to be certain that these growths in the ureter are not the result of secondary spread from the bladder cancer (Greene, Hayllar and Bogash, 1958).

A disturbing feature of carcinoma of the ureter is its poor prognosis and this may be, at least partly, the result of the delay between the onset of symptoms and treatment. In the study by McIntyre and his associates (1965) the average delay was 35 weeks, but in earlier series it has been as long as 2 years (Abeshouse, 1956; Greene, Hayllar and Bogash, 1958). The reasons suggested for the delay include procrastination by the patient or his family doctor, inconclusive investigations or incorrect assessment, and the decoy of finding a bladder tumour sufficient to account for the haematuria, or a co-existent urinary calculus.

In this prospective study we present the findings in 54 patients with transitional cell carcinoma of the ureter, which we believe is the largest personal series so far recorded (all patients having

been seen, examined and recorded by one of us). The cases were collected over a 20-year period and graded histologically in accordance with the method adopted by the Bristol Bladder Tumour Registry (Miller, Mitchell and Brown, 1969). Tumours arising from tissues other than transitional epithelium (for example, pedunculated fibrolipomata) have been omitted from the study. During this period 2 benign tumours arising from tissue other than transitional epithelium have been seen and these were easily treated by local excision, as is well documented elsewhere (DeKlotz and Young, 1964; Parker, 1968; Knackstedt, Pirozynski and Oliver, 1971). They have not been included in the 54 cases studied. Similarly, malignant tumours secondarily invading the ureter from surrounding structures have also been omitted. Tumours of the renal pelvis and cases where tumours were found initially in both renal pelvis and ureter have been excluded and will be reported elsewhere.

Patients

All cases of transitional cell carcinoma of the ureter referred to the United Bristol Hospitals and Southmead General Hospital during the period 1951-1970 have been included in this study. The patients fall naturally into two groups:

1. Those with primary carcinoma of the ureter with no previous history or investigative evidence of urothelial tumours in other parts of the urinary tract. There were 34 patients in this group.
2. Those with either a past history of bladder tumour or a bladder tumour found at the time of diagnosing the ureteric lesion. 20 patients were in this group, of which 4 had bladder and ureteric tumours found at the same time.

Grading and Staging

The tumours were staged postoperatively according to the invasion of the muscle wall and the presence of distant metastases, and they were graded into 3 histological grades (Miller, Mitchell and Brown, 1969).

Malignant Tumours

Low-grade lesions are more than 5 cells thick with regular basement cells, showing a palisade appearance and some variations in the size and shape of cells and nuclei.

Average-grade lesions are more than 5 cells thick, with basement cells irregular in size and shape and nuclei tending to be circular. The cells are similar in all layers with little differentiation, but some variations in the shape and depth of staining of the nuclei are present.

High-grade lesions are just identifiable as transitional cell epithelium with no differentiation into layers. Basement cells are not identifiable and there is a great variation in size and shape of the cells and nuclei. Tumour giant cells are frequently seen and many darkly staining nuclei are present.

Benign Tumours

The criteria for grading as a benign urothelial tumour are less than 5 cells thick, with regular basement cells and showing a palisade appearance. The fronds may be long, but there is no variation in the size and shape of the cells or nuclei.

Relative Incidence

During the 20-year study period there were 54 cases of carcinoma of the ureter and 2,770 cases of carcinoma of the bladder admitted to the Bristol Bladder Tumour Registry. This gives an approximate ratio of 1 case of carcinoma of the ureter for every 51 cases of carcinoma of the bladder. During the same period 43 cases of transitional cell carcinoma of the renal pelvis were admitted to the same hospitals.

Group 1—Primary Carcinoma of the Ureter

Of the 34 patients in this group, 14 had low-grade tumours (average age 62 years), 15 average-grade tumours (average age 66 years), and 5 high-grade tumours (average age 64 years). The ages of the patients ranged from 43 to 79 years. 23 patients were male and 11 were female and no significant difference in this ratio of 2 to 1 was found between the three grades. 12 patients presented during the period 1951-1960 and 22 during the 10 years 1961-1970.

(a) *Presenting Symptoms*

31 patients presented because of haematuria and the remaining 3 cases were found during investigations for frequency and dysuria. The average duration of haematuria before presentation was 4.5 months. However, for patients with low-grade tumours the average period was 8.0 months, compared with 2.5 months for the combined average- and high-grade groups. This may be due to patients with average- and high-grade tumours complaining of other symptoms more often than patients in the low-grade group: 7 presented with loin pain, 8 had either backache or abdominal pain, and 12 complained of incidental symptoms of bladder outflow obstruction.

(b) *Signs*

Half the patients had a palpable kidney on the affected side and it is of note that 14 of these 17 cases had either average- or high-grade tumours (Table I). The palpable kidney was associated

Table I

Histological Grading of 34 Cases of Primary Carcinoma (Group 1) of the Ureter to show Incidence of a Palpable Kidney

Grade	Total Number	Total with a Palpable Kidney
Low	14	3
Average	15	10
High	5	4
	34	17

with a poor prognosis as all but 4 patients had died within 4 years of diagnosis. Of these 4 patients, 1 with a low-grade tumour died, 8 years later, from a recurrence in a ureteric stump, having had a nephro-ureterectomy without excision of the ureteric orifice; 2 with average-grade tumours were alive 2 and 4 years respectively after treatment and 1 patient with a low-grade tumour was alive and well 2 years after treatment.

(c) *Investigations*

(i) *Urine*

A midstream specimen of urine collected from the 34 patients at their first attendance showed red blood cells in 15 samples, and a significant urinary infection in only 3.

(ii) *Excretion Urography*

Excretion urography was not performed on 4 patients. Three of the 4 were referred from other hospitals when recurrent haematuria followed a nephrectomy performed for what had been

diagnosed as a benign hydronephrosis, though the obstructing factor had not been identified. The fourth presented with severe abdominal pain and a painful mass in the right upper abdomen. A diagnosis of empyema of the gall bladder was made and she was explored before excretion urography was carried out. In 28 of the remaining 30 patients, the findings at urography indicated a pathological lesion requiring an urgent diagnosis (Table II). These abnormalities were particularly obvious in patients with average- and high-grade tumours, where 14 of the 16 patients

Table II

Findings on Excretion Urography (Group 1)

	Total (30)	Low (14)	Average (12)	High (4)
Findings:				
(i) Non-functioning kidney	18	4	10	4
(ii) Hydronephrosis	4	3	1	0
(iii) Space-occupying lesion	6	5	1	0
Total with abnormal findings)	28	12	12	4
(No abnormal findings	2	2)		
Total	30			

studied had non-functioning kidneys. One of the remaining 2 in this group had a hydronephrosis demonstrated on I.V.P., and the other had an obvious tumour in the ureter.

One patient was found to have a renal calculus and this led to a delay in making a correct diagnosis.

(iii) *Retrograde Pyelography and Ureterography*

The earlier cases were studied by retrograde pyelography and later cases by retrograde ureterography using Braash or Chevassu bulbs. This investigation was not carried out on 14 patients where the results of excretion urography and cystoscopy had left no doubt as to the diagnosis. In fact, in only 1 patient of 3 with inconclusive pyelo- or uretero-graphic results was the diagnosis still in doubt. There was no delay in the treatment of this patient as the clinical findings and investigations were considered suspicious enough to warrant exploration of the kidney and ureter.

(iv) *Cystoscopy*

Blood was seen at the ureteric orifice in 5 of the 34 patients, and in a further 6 cases actual fronds of tumour were seen protruding from the ureteric orifice. In these 11 cases the lesions were in the lowest third of the ureter.

(d) *Delay in Diagnosis*

The average period between presentation and treatment was 4 months 10 days, but in 5 cases the diagnosis was greatly delayed by factors that could have been avoided. Three patients were delayed 26, 10 and 9 months respectively, when a kidney had been removed for hydronephrosis, leaving the causative carcinoma of the ureter *in situ*. These 3 patients were referred to our Department when further haematuria occurred after the nephrectomy. We have seen no similar case during the last 15 years.

Another serious delay of 20 months was the result of misdiagnosis of a urogram due to the decoy of a small stone in the renal pelvis, and a fifth patient refused treatment for 10 months.

(e) Position of the Tumours (Table III)

19 tumours were in the lowest third of the ureter and in 2 cases almost the whole ureter was affected. 19 tumours were on the right and 15 on the left.

Table III

Position of the Lesions (Group 1)

	Total (34)	Low (15)	Average (14)	High (5)
Upper third	7	5	1	1
Middle third	6	2	4	0
Lowest third	19	8	7	4
Whole length	2	0	2	0

(f) Type of Operation (Table IV)

The variety of surgical procedures used were the result of changes in technique over the 20-year period, variations in the position and stage of the lesion, and differences in the age and physical state of the patients. The operation of choice during the period under study was nephro-ureterectomy, but partial ureterectomy was carried out in 7 patients. Three had previously had a

Table IV

Type of Operation carried out (Group 1)

Nephro-ureterectomy with cuff of bladder	14
Nephro-ureterectomy with cuff of bladder + D.X.T.	4
Nephro-ureterectomy with no cuff of bladder	8
Nephro-ureterectomy with no cuff of bladder + D.X.T.	1
Resection of part of ureter (cuff removed)	5
Resection of part of ureter + D.X.T. (no cuff)	2
	34

nephrectomy for hydronephrosis and the remaining 4 had resection of the lower part of the ureter; 1 because of a temporary cardiac arrest during the operation, in 2 the choice was influenced by the ages of the patients (79 and 83 years respectively), and 1 had a planned resection. Repeated radiological demonstrations of the ureter have shown no recurrence in the remaining portion in this last patient and she is alive and well 5 years after operation.

(g) Subsequent Development of Bladder Carcinoma (Table V)

11 of the 34 patients subsequently developed bladder tumours and they occurred with equal frequency in the 3 histological grades. Of 23 patients who had a cuff of bladder removed with the ureter, only 6 developed bladder tumours, but 5 out of the 11 patients who had no cuff removed developed bladder carcinomata. In 9 patients the bladder tumours appeared in the proximity of the ureteric orifice which had drained the tumour-bearing ureter before ureterectomy. Four of those who subsequently developed bladder tumours showed a higher grade of tumour in the bladder than had previously occurred in the ureter, suggesting that this was probably a new tumour rather than a recurrence (Miller *et al.*, 1969). The grading of the ureteric tumours at

ureterectomy and the grading of the subsequent bladder tumours were the same for the remaining patients.

Table V

Incidence of Subsequent Bladder Carcinoma (Group 1)

	Total	Cuff of Bladder removed	No Cuff of Bladder removed
Developed bladder carcinoma	11	6	5
No bladder carcinoma	23	17	6

Group 2—Ureteric Tumours in association with Bladder Tumours

Of the 20 patients in this group, 11 presented during the first 10 years under study and 9 presented during the second decade. 17 had low-grade tumours, 2 had average-grade tumours and 1 had a high-grade tumour. Eight were male and 12 female, with an average age of 62 years (Range: 31-76 years).

The average period between diagnosis of the bladder tumour and the subsequent detection of a tumour in the ureter was 4 years 10 months. Although it is routine policy to investigate all bladder tumours by intravenous pyelography, a second pyelogram would not normally be carried out within 5 years unless the first pyelogram was suspicious or further haematuria occurred in the absence of any obvious cause in the lower urinary tract. In 15 cases the bladder tumours had been situated near the orifice of the involved ureter. 11 lesions were in the left ureter and 9 in the right. 13 tumours were in the lowest third of the ureter, 3 in the middle third, 3 in the upper third, and 1 patient had multiple tumours. The tumours in the ureter were of a higher grade than the previous tumours in 2 cases, but the remaining 18 patients had tumours of the same grade.

Six patients, including the 3 with high- and average-grade lesions, had a palpable kidney and again it was a sign of a bad prognosis. The patient with tumours of high grade died from metastases within 6 months of diagnosis. One patient with an average grade tumour died during the sixth year from metastases, but the other is alive and well after 8 years. Two patients with low-grade tumours died within 12 months of diagnosis, 1 from a pulmonary embolus, and the other from acute pyelonephritis. The third is alive and well after 10 years.

Half the patients in this group had conservative operations resecting only the portion of the ureter containing the growth. Three of these operations were carried out in the 11 patients who presented during the first decade of the study—1 patient had a solitary kidney, and for 2 patients the treatment was palliative. During the second decade a conservative approach was adopted for 7 of the 9 patients who presented during this period.

19 patients were available for follow-up. Three died during the postoperative period, 2 are symptom-free after 5 and 7 years, and the remaining 14 developed further bladder tumours. Three of these bladder tumours are of a higher grade than the ureteric lesion and 11 are unchanged.

Of the 10 patients who had conservative operations, 4 are dead, 1 from pneumonia and 2 from coronary thromboses 2 and 18 years after treatment. No evidence of metastatic tumour was found at postmortem. The remaining patient who had a palliative resection for a high-grade tumour with metastases died 6 months after operation. The other 6 patients are alive and well an average of 7 years after treatment.

Prognosis

For the 34 patients with primary carcinoma of the ureter, the post operative survival was directly related to both histological grading and the degree of spread (Table VI). Once invasion of the

muscle wall had occurred, the prognosis deteriorated dramatically. In the 21 cases where invasion had occurred, 15 died from metastatic spread within a short period of time, 2 died from other causes and 4 are alive 10 years, 3 years, 2 years and 18 months after treatment. Of the 13 cases with no invasion, only 2 died from metastases, 3 died from other causes and 8 are alive and well an average of 5 years after treatment.

Table VI

Survival of 54 Patients with Ureteric Tumours (Groups 1 and 2)

(For convenience the figures are expressed as a percentage)

Grade

	Primary Tumours			Tumours following Bladder Tumours
	Low	Average	High	
5 years	45%	10%	0	65%
10 years	15%	0	0	31%

Stage

	Primary Tumours		Tumours following Bladder Tumours	
	No Invasion	Invasion Present	No Invasion	Invasion Present
5 years	42%	15%	77%	50%
10 years	18%	0	56%	0

The patients with a previous history of bladder tumours had a better prognosis (Table VI). Only 4 patients had evidence of invasion through the muscle coat and they fared worse than the rest.

Discussion***Incidence***

In 1956 O'Connor concluded from a study of his own series of cases and the world literature that there had been a marked increase in the incidence of primary ureteric carcinoma. He claimed also that sufficient evidence was available to prove that this was not entirely the result of improved diagnostic procedures. A similar increase in incidence has since been demonstrated by Bloom, Vidone and Lytton (1970), who collected 102 cases treated at 13 different hospitals over a 30-year period and found that 86 presented during the second half of the period under study. This trend was noted in our relatively small but personal series of primary tumours, with 12 patients presenting during the first decade, compared with 22 during the second. The advances in excretion urography and retrograde ureterography during the past 20 years, plus the development of more urological units must have ensured that the diagnosis is now rarely missed.

When the ureteric growth occurred in association with bladder tumours, no increase in incidence was evident as 11 patients presented during the first decade and 9 during the second. This is surprising, as it might have been anticipated that in the earlier period the bladder tumour could well have masked the development of symptoms and signs of the ureteric growth because investigations (such as ureterography) had not been developed.

Sex

In our study primary tumours of the ureter occurred twice as frequently in males, and this is in accordance with a collection of 454 cases from the literature (Abeshouse, 1956) and a series from Leeds (McIntyre, Pyrah and Raper, 1965). However, several studies in North America report a much higher incidence in males, varying from 3 : 1 to 5.5 : 1 (Whitlock, McDonald and Cook, 1955; Bloom, Vidone and Lytton, 1970; Hawtrey, 1971). The reason for this difference is obscure but, in contrast, those of our patients who had a prior history of bladder tumour showed a male to female ratio of 1 : 1.

Side and Site

We also confirm that there is no predilection to side for the lesion and that more than half the tumours occur in the distal third of the ureter. It is of interest to record that those tumours in the lower third are more likely to present with blood at the ureteric orifice on cystoscopy and, amongst the secondary tumours (*i.e.* those presenting with bladder tumour before or at the same time), 17 out of 20 were in the lower third. Does this indicate reflux seeding on to adjacent urothelium or does it indicate a localised area of unstable mucosa of the bladder wall, extending into the lower third of the ureter?

The Kidney above the Ureteric Tumour

In 23 of our 54 patients the affected kidney was palpable and this was associated with a more active tumour and a very poor prognosis. Other authors have reported that less than 10% of their patients had a palpable kidney, but they included benign tumours in their studies and this, in part, may have influenced their findings (Riches, Griffiths and Thackray, 1951; McIntyre *et al.*, 1965; Bloom, Vidone and Lytton, 1970).

It would therefore appear that the more malignant tumours produce complete obstruction of the ureter sooner than the more benign lesions and a tense, palpable, hydronephrotic kidney is found when the patient presents for examination. Out of 22 hydronephrotic kidneys (4 functioning and 18 non-functioning), no less than 17 were palpable, whereas, in other circumstances, a hydronephrosis can often develop to massive proportions and yet nothing more definite than a fullness in the loin can be felt. Out of 17 palpable kidneys amongst the 35 carcinomas of ureter, 13 kidneys were non-functioning on the intravenous pyelogram. Where the kidneys were both palpable and non-functioning all the patients were dead within 85 months and the average survival time was only 25 months.

Abeshouse (1956) claimed that excretion urography was of relatively little diagnostic value in carcinoma of the ureter, but in the present series the pyelographic findings in 28 of the 30 patients examined with primary lesions suggested serious pathology requiring urgent investigation. During the 15-year period since Abeshouse's paper the significant advances in the technique of urography have contributed to our results. A non-functioning kidney, which was the commonest finding (Badenoch, 1965), indicated a more malignant tumour with a poor prognosis. This has previously been suggested by Tresidder and Warren (1954), who analysed a small series of cases, and has since been well demonstrated by Bloom, Vidone and Lytton (1970). Again, it is probably the result of early complete obstruction of the ureter by a carcinoma rather than the partial obstruction found with a more benign lesion.

MacLean and Fowler (1956) claimed that a high incidence of calculi is found with tumours of the ureter. We did not find this and believe that their assumption was due to their very small numbers and the inclusion of squamous cell carcinomata in their series. Only 1 of our patients had a co-existing urinary calculus, but its presence in an otherwise normal urogram caused a delay in diagnosis of 20 months.

Delay in Diagnosis

An average delay of 2 years from the onset of symptoms to treatment was found in cases collected from the literature (Abeshouse, 1955), but our delay was 8.5 months and is similar to other more recent studies (McIntyre, Pyrah and Raper, 1965). We believe that the relative improvement is the result of increased awareness of the condition and the improvement in the techniques of investigation. We hope that it will eventually lead to an improved prognosis. In our series there were 3 cases with delays in diagnosis when hydronephrotic kidneys were removed for what were believed to be benign conditions, the offending ureteric tumours being left *in situ*. The correct diagnoses were made and treatment carried out when further haematuria occurred. Haematuria is noted in 20% of patients with benign hydronephroses (Roberts and Slade, 1964), but we feel that when an obvious obstructed kidney and ureter is found and the renal pelvis contains blood, then exploration of that ureter is mandatory.

In none of our series were we able to determine any history of *contact with carcinogenic agents*, such as betanaphthylamine as described in ureteric neoplasia by Poole-Wilson (1969), nor have we any incidence of tumours developing in the upper urinary tract after total cystectomy (Wallace, 1969). There were no bilateral ureteric tumours in this series.

The *indications for the various operations* carried out in our study will not be discussed in detail, but the best prognoses followed a one-stage nephro-ureterectomy removing a cuff of bladder. To ensure removal of the entire intramural ureter the cuff of bladder is removed by an intravesical approach with a purse-string suture placed around the ureteric orifice to prevent contamination of the bladder by neoplastic cells (Mitchell, 1969). This should be done before any surgical manipulation of the lower ureter. Having closed the orifice with a purse-string, the intramural ureter can be dissected from inside the bladder, which is a comparatively easy approach for this otherwise awkward dissection.

Subsequent Appearance of Bladder Tumours

11 of the 34 patients with primary ureteric tumours developed bladder tumours after an average period of 13 months and, like Kinder and Wallace (1962), we found it occurred more frequently when the intramural portion of the ureter was not removed.

This high incidence of bladder tumour associated with carcinoma of the ureter has been well documented (Greene, Hayllar and Bogash, 1958; Hawtrey, 1971) and in our study it occurred with equal frequency in the 3 histological grades. Bloom, Vidone and Lytton (1970) recorded urothelial recurrences in 20% of their 102 patients with ureteric tumours after a mean period of 19 months, but the majority of these occurred after low-grade tumours of the ureter, and they suggest that this is due to the longer survival of these patients.

Our *treatment for patients with carcinoma of the ureter following tumours of the bladder* has varied during the past 20 years. During the first decade the radical operation of nephro-ureterectomy was practised exclusively, but, in view of the possibility of the entire urothelium being unstable and liable to malignant change in any part, even in the opposite kidney or ureter (Wallace, 1972), we now follow a more conservative policy in removing only the tumour and some adjacent normal ureter, provided ureterography shows no evidence of any further active lesions. Although the follow-up period is still short, the more conservative approach has not reduced the survival figures, which appear to be consistent in both decades.

The *prognosis* for our 54 patients was directly related to the histological grading of the tumour and, like others, we found that survival is markedly reduced once invasion of the muscle coats has occurred (Whitlock, McDonald and Cook, 1955; Bloom, Vidone and Lytton, 1970; Hawtrey, 1971). The reasons for the better prognosis for patients in Group 2 must include the fact that the majority of lesions (17 out of 20) were low grade and these patients are constantly reviewed after their bladder tumours are diagnosed.

Summary

A prospective study of a personal series of 54 cases of carcinoma of the ureter that presented over a 20-year period is reported.

There has been an apparent increase in the incidence of primary carcinoma of the ureter, but the diagnosis is being made earlier because clinicians are more aware of the condition and better techniques for investigation are available.

The prognosis for carcinoma of the ureter was directly related to the histological grading used by the Bristol Bladder Tumour Registry.

A marked reduction in survival was associated with a palpable kidney, non-function of the kidney and evidence of invasion of the muscle coat.

A third of the patients with primary carcinoma of the ureter subsequently developed bladder tumours and the risk was increased when the intramural portion of the ureter was left *in situ*. A method of excising the intramural portion of the ureter is mentioned.

Recently we have carried out more conservative operations for carcinomata of the ureter occurring after treatment for carcinoma of the bladder, and the results are encouraging.

We wish to convey our sincere thanks to Mr Norman Slade and Mr Michael Roberts for their kindness in allowing us to examine and report a number of their patients, whose details have been included in this series, and for the encouragement and constructive criticism of this analysis in the past. We also wish to thank Dr Norman Brown, Dr Alan Hunt and, more recently, Dr Richard Blight for their help and advice on the histology.

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Application of Renal Autotransplantation to the Treatment of Simultaneous Bilateral Ureteral Tumours

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The multicentric origin of transitional cell carcinoma in the urinary tract is too well known to require further comment. That this process can and frequently does involve the upper tracts bilaterally is also well appreciated and accounts for an increasing trend toward the conservative in management of lower grade tumours (Vest, 1945; Harvard and Evans 1964; McIntyre, Pyrah and Raper, 1965; Bloom, Vidone and Lytton, 1970; Petkovic, 1972). This paper records autotransplantation as a method for conservation of renal tissue in such a case, a procedure necessitated by extensive ureteral involvement.

Case Report

A 65-year-old white female looking considerably younger and in good general health had been successfully treated over 4 years for recurrent low grade papillary carcinomata of the bladder. The treatments had consisted mainly of transurethral resection and fulguration. When the lesions finally became too numerous, the patient was referred for cystectomy; but it quickly became apparent she would not accept a urinary diversion, particularly one involving a stoma. Topical Thiotepe was tried mainly as a temporising measure but on follow up cystoscopy the improvement was striking and there was only 1 remaining small lesion which was fulgurised. Unfortunately with each peristalsis of the left ureter, a papillary tumour projected from the orifice, which on biopsy was grade II transitional cell carcinoma. The left renal function was normal but a left retrograde pyelogram demonstrated tumour involvement of about the lower half of the ureter (Fig. 1). Right renal function was decreased due to chronic reflux and there was a tumour in the mid ureter (Fig. 2) which due to ureteral elongation was treatable by sleeve resection. 24-hour creatinine clearance was 70 cc/minute. A transureteroureterostomy was planned in order to salvage the better left kidney but at surgery the intraluminal mass extended higher than anticipated and after resection with a safe margin only the upper third of the left ureter remained. When the right ureteral tumour had been excised and the anastomosis completed, there was no excess slack and the left ureter would not reach across the midline without tension. There was no evidence of local or distant spread and the patient's condition was good. 25 g of mannitol and 10,000 units of heparin were given and a left renal autotransplantation done. There were 2 renal arteries which were handled in the following manner: the upper and larger was anastomosed end to side to the common iliac; the lower and smaller was spatulated and anastomosed end to end to the left hypogastric artery. All pulses were excellent and urine formation on the left began during the ureteral re-implantation. Follow-up examination revealed a good functional result (Fig. 3). The patient has remained in good health with no sign of recurrence since the original operation was performed 1 year ago.

Comment

Many authors have alluded to the occurrence of bilateral transitional cell tumours of the upper tracts (Vest, 1945; McIntyre *et al.*, 1965; Bloom *et al.*, 1970; Petkovic, 1972). Harvard and Evans (1964) commenting on their case of bilateral tumours of the renal pelvis stated, "Perhaps it might be worthwhile to consider a more conservative surgical approach in selected tumours of the renal pelvis and ureter. Vest (1945) has expressed similar views only to be decried by many." In the case presented conservative surgery was indicated by the bilaterality of the tumours and



Fig. 1



Fig. 2

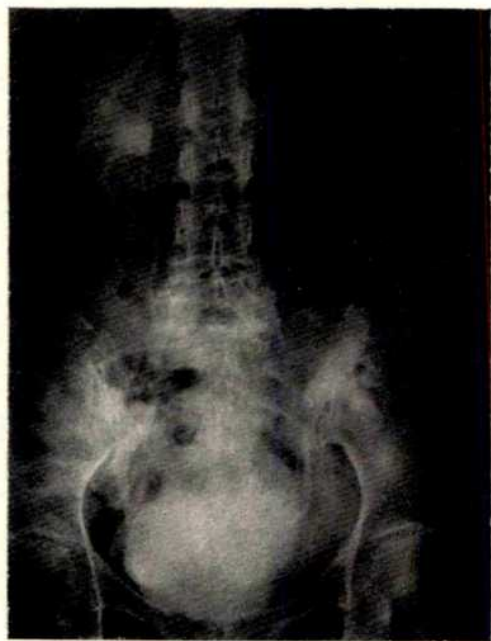


Fig. 3

Fig. 1. Left retrograde showing ragged lower ureter with highest definite filling defect at level of mid ureter.

Fig. 2. Cystogram with right ureteral filling by reflux. Demonstrates ureteral elongation due to chronic reflux and filling defect at mid ureteral level.

Fig. 3. Follow-up IVP showing functioning transplant in left iliac fossa.

the decreased renal function on the refluxing right side. Sleeve resection, transuretero-ureteros-tomy or ureteroneocystostomy with or without bladder flap are preferable, of course, where possible. A high ileal loop diversion would also be satisfactory although rejected by this particular patient. Interposition of an ileal loop between ureter and bladder is generally unsatisfactory because of reflux, infection, and declining renal function. That renal autotransplantation is preferable is supported in a case report by Murphy, Staub and Kenny (1972), and in the present case certainly appeared to be the best alternative. Since first reported by Hardy in 1963 autotransplantation has been gaining sporadic acceptance in the management of difficult ureteral problems and renal arterial obstructions (Hardy, 1963; Marshall *et al.*, 1966; Kaufman, Alferez and Navarrete, 1969; Linke and Hay, 1972; Murphy *et al.*, 1972). There will be occasional situations where it is applicable, justifiable and logical. It is part of the urological surgical armamentarium and should not be dismissed as too bizarre.

Summary

A case of simultaneous bilateral ureteral tumours is presented in which renal autotransplantation was used to solve a problem in renal conservation and urinary tract reconstruction. Ureteral tumours warrant at least the consideration of conservative management and renal autotransplantation should be kept in mind as a legitimate urological procedure where simpler methods will not suffice.

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Primary Tumours of the Ureteric Stump

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After nephrectomy for non-malignant disease, primary tumours of the ureteric stump are extremely rare and present a significant diagnostic problem. In several reviews and isolated case reports, 14 such cases have been described (Andronaco and Brown, 1972).

Four additional cases were mentioned briefly in a comprehensive study of 42 symptomatic ureteric stumps encountered at the Mayo Clinic (Malek *et al.*, 1971). A detailed description of these 4 cases and further considerations basic to the diagnosis and management of such patients are herein presented.

Report of Cases

Case 1. A 71-year-old man had undergone left nephrectomy and partial ureterectomy for pyonephrosis in 1936. He returned a year later complaining of symptoms suggestive of urosepsis as well as gross haematuria and pain in the left groin. Cystoscopy and a left retrograde ureterogram disclosed that the previously normal-appearing lower ureter contained a tumour-like filling defect. On exploration, the left ureteric stump and regional lymph nodes were found to be involved by a poorly differentiated papillary transitional cell carcinoma and were excised. Two years later he died of carcinomatosis.

Case 2. A 64-year-old man, whose right kidney and upper ureter had been removed for chronic atrophic pyelonephritis in 1937, presented with gross painless haematuria 1 year postoperatively. Cystoscopy and a retrograde ureterogram of the right stump showed the previously normal-appearing right lower ureter to contain a filling defect with dilatation of the proximal portion (Fig. 1). The ureteric stump was totally excised; it contained a moderately well-differentiated, partially infiltrating papillary transitional cell carcinoma (Fig. 2). The patient died 8 years later of heart disease.

Case 3. A 64-year-old man underwent left nephrectomy and partial ureterectomy for chronic atrophic pyelonephritis in 1936. Two years later, at the time of cystoscopic re-check of an infrequently recurring, well-differentiated transitional cell carcinoma of the bladder, he presented with gross, painless haematuria. A recurrent bladder tumour was fulgurated and a left retrograde ureterogram of the stump disclosed a filling defect in the lower third of the previously normal-appearing left ureter. The left ureteric stump was totally removed; it contained a well-differentiated, noninfiltrating papillary transitional cell carcinoma. He died 3 years later of heart disease.

Case 4. A 59-year-old man who had undergone left nephrectomy and partial ureterectomy for cystic hydro-nephrotic kidney in 1945 was being re-checked regularly for a recurrent moderately well-differentiated papillary transitional cell carcinoma of the bladder. He was found to have a tumour protruding from the left ureteral orifice 4 years postoperatively. The left ureteric stump was completely excised; it was found to be studded with multiple, noninfiltrating, urothelial tumours of papillary transitional cell carcinoma (Fig. 3). The patient died 6 years later of carcinomatosis.

Comment

After nephrectomy and partial ureterectomy for conditions other than urothelial carcinomas, approximately 1% of the remaining ureteric stumps produce symptoms. The incidence of transitional cell carcinoma developing *de novo* in these stumps approaches 10% (Malek *et al.*, 1971).

Several aetiological factors for malignant changes, including chronic inflammation, leukoplakia, transformation in inclusions migrating from basal layers of the urothelium, and carcinogenic substances, have been mentioned (Bergman, 1967). Whatever the cause, it is essential to remember that the ureteric stump remains as an integral part of the urinary tract and is just as likely to become diseased.

Abnormalities of the uretero-vesical complex, operative neurovascular damage to the ureter, and retrograde peristalsis in obstructed or diseased ureters help to explain why a ureteric stump can be a direct extension of the bladder cavity and hence its potential, as that of the rest of the urinary tract, for primary malignant change. In effect, a ureteric stump may be considered to be a vesical diverticulum, a useful analogy amply supported by the close similarity of the incidence



Fig. 1 (case 2). Right retrograde ureterogram disclosing grossly dilated ureteric stump containing a filling defect.



Fig. 2 (case 2). Surgical specimen shows ureteric stump involved by tumour in its lower portion.

of primary urothelial carcinomas in both structures (McLean and Kelalis, 1968; Malek *et al.*, 1971). However, in contrast to vesical diverticula, the ureteric stumps are only rarely visualised on excretory urography and thus tend to be forgotten. Lack of urine flow and pathologic obstruction may substantially delay the clinical manifestation of the disease brewing in such cul-de-sacs.

Five of the 42 patients with symptom-producing stumps reviewed at the Mayo Clinic had presented with gross haematuria; 3 of these 5 patients had a primary stump tumour and 2 of the 3 had recurrent bladder tumours of the same variety (Malek *et al.*, 1971). Thus, gross haema-

turia in a patient with ureteric stump is highly suggestive of neoplastic change. Every patient who has a ureteric stump and who becomes symptomatic should be fully investigated, including careful determination of the status of the ureteric stump, regardless of pathologic findings elsewhere. Retrograde ureterography of the stump and cytologic examination of its washings are mandatory. Infrequently, when the ureteric stump cannot be visualised by retrograde studies and especially in the presence of gross haematuria of undetermined cause, exploration and complete excision of the stump is advisable.

If possible, total removal of the tumour-bearing stump and the involved lymph nodes is the

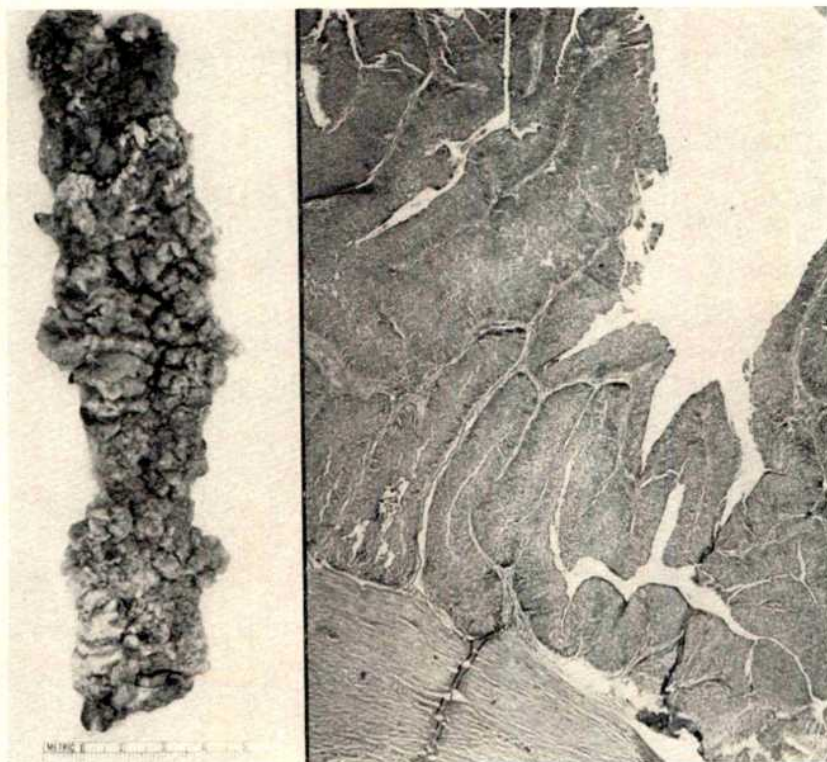


Fig. 3. (case 4). *Left*, Surgical specimen shows entire left ureteric stump studded with papillary carcinoma (From Malek, R. S., Moghaddam, A., Furlow, W. L. and Greene, L. F. (1971). Symptomatic ureteral stumps. *Journal of Urology*, **106**, 521-528. By permission of Williams & Wilkins Company). *Right*, Section of specimen shows moderately well-differentiated papillary transitional cell carcinoma without infiltration of ureteral muscle wall. (Hematoxylin and eosin. $\times 26$.)

treatment of choice in the absence of distant metastasis. Prior to exploration, retrograde distention of the stump with saline may make the identification and dissection easier. Malignancy in the ureteric stump and vesical neoplasm are not mutually exclusive. In a patient who has or has had a vesical neoplasm, the ureteric stump should not be left if nephrectomy is contemplated. Furthermore, if a patient with a ureteric stump develops a bladder tumour, prophylactic excision of the stump should be seriously considered.

The results of treatment have been gratifying: 2 patients died of carcinomatosis 2 and 6 years later but the remaining 2 survived for 3 and 8 years, only to die of heart disease with no evidence of recurrent or residual tumour. Regular follow-up, akin to that for bladder tumour patients, is recommended for these patients regardless of the presence or absence of a bladder tumour.

Summary

Four cases of transitional cell carcinomas developing *de novo* in ureteric stumps remaining after nephrectomy and partial ureterectomy for non-malignant causes are presented.

The ureteric stump should be considered an extension of the bladder cavity.

Pathologic findings elsewhere in the urinary tract should not divert the attention of the urologist from the stump.

Complete excision of the tumour-bearing stump with its regional nodes is the treatment of choice.

Prophylactic excision of the ureteric stump in a patient who develops a bladder tumour should receive serious consideration.

The results of treatment were encouraging: all 4 patients remained alive for at least 2 years and 2 lived beyond 5 years.

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The Ureter in Posterior Urethral Valves

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In previous papers we have described our experience with the general management of over 200 boys with posterior urethral valves (Williams *et al.*, 1973) and discussed the problem of incontinence of urine (Whitaker, Keeton and Williams, 1972). It remains to review the other main postoperative problem which is the investigation and management of the dilated ureters.

How well the kidneys function after relief of the valvular obstruction and whether there is any further deterioration depends on the interplay of several factors (Fig. 1). In practice, by far

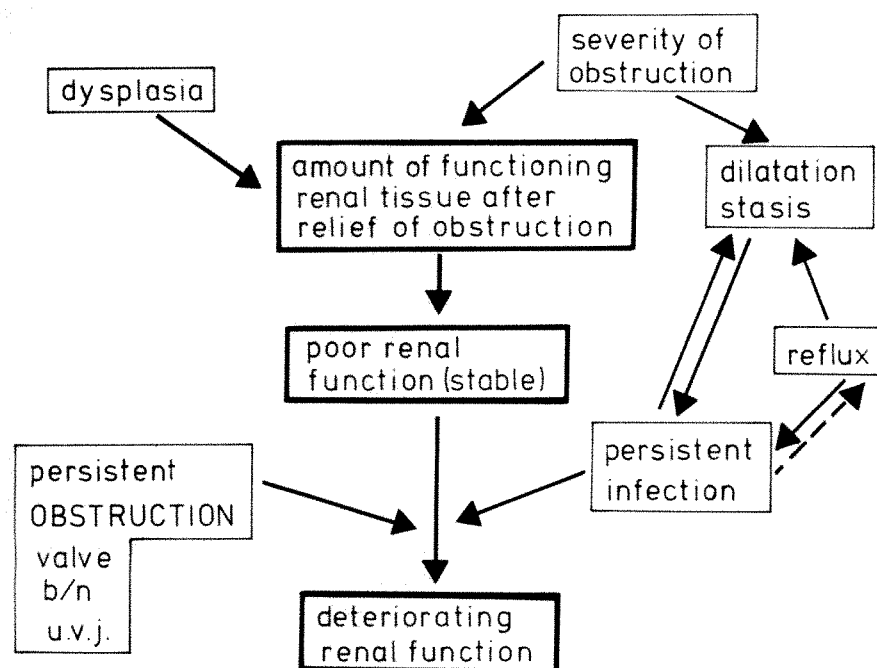


Fig. 1. Factors bearing on the renal function after relief of valvular obstruction in boys with posterior urethral valves.

the most difficult factor to assess is whether or not there is a significant degree of ureteric obstruction at the ureterovesical junction and in this context the standard investigations of intravenous and retrograde urography leave much to be desired. They are of limited value and at times may be misleading. There is a need for a more accurate means of assessing obstruction.

It is impossible to define the meaning of obstruction without reference to pressures and flows as a narrowing in any fluid-filled system will become a significant obstruction only if it is necessary to raise the proximal pressure to obtain the same flow rate through the narrowed segment.

This work was performed whilst the author was a senior registrar at The Institute of Urology, London and The Hospital for Sick Children, Great Ormond Street, London.

Similarly, in the ureter it is not possible to make a definite diagnosis of obstruction at any level without information concerning the pressures and flows.

This paper will describe the results of a technique which obtains the relevant information needed to diagnose ureteric obstruction in these boys with posterior urethral valves, and will emphasise the shortcomings of the more standard methods of investigation.

Methods

In the follow-up period after ablation of the valves all the boys had biochemical assessment of the overall renal function and radiographic assessment of the state of the urinary tract. Intravenous urograms were carefully supervised and the kidneys and ureters were screened on an image intensifier when it was deemed necessary or helpful. The degree of dilatation of the upper tracts and the delay in appearance and disappearance of the contrast media were noted and compared with previous films.

Micturating cystograms were routinely performed postoperatively to assess the ability of the bladder to empty and to diagnose or exclude vesico-ureteric reflux.

A few boys had retrograde pyelograms or ascending ureterograms. From these the patency of the ureterovesical junction was assessed and the rate of ureteric emptying observed both supine and erect.

Finally, in a small and selected group of these boys a fuller urodynamic assessment was made. Details of this method of assessment can be found elsewhere (Whitaker, 1972, 1973). The ureters are perfused *in situ* at a known flow rate and the pressure which is needed to maintain this flow rate is measured. The perfusion and pressure measurements are both carried out through the same single channel, which can be either a nephrostomy tube, if such a tube is already in the kidney, or a needle inserted transcutaneously into the kidney. Alternatively, at the time of exploration of the lower ureter the same procedure can be applied by temporarily occluding the ureter and perfusing the lower segment via a small needle. Five studies were performed via a nephrostomy tube, 9 via antegrade puncture of the kidney and 3 via puncture of the lower ureter at open operation.

If the procedure is being done under X-ray control the perfusion fluid is a dilute contrast medium so that additional, visual information can be obtained concerning peristalsis, distensibility and areas of hold-up. Early in the series a variety of contrast media was used (Table), but more recently only 35% Diodone and 25% Hypaque have been employed. The viscosities of these fluids are different from saline and it is important to be aware of this when interpreting the results.

Perfusion is continued at a rapid rate, usually 10 ml/min, until the pressure stabilises. At this point there is a constant known flow throughout the system and into the bladder and this equilibrated pressure is noted. This high flow rate is used to "stress" the system to its maximum and also to make any intrinsic flow from the kidney relatively unimportant.

Additional information is obtained if the bladder is catheterised, as the bladder pressure can be subtracted from the ureteric pressure to give a "pressure drop" across the ureteric orifice. Furthermore, by filling the bladder to increasing volumes it is possible to see how the ureteric orifice behaves under these varying conditions.

In the early investigations the bladder was drained freely throughout the test and the pressure within the bladder not measured. These results were expressed as "absolute" pressures with the point of reference at the level of the kidney outside the body. Other boys had the bladder pressure measured under varying degrees of bladder filling and "relative" pressures were obtained, representing the drop in pressure across the ureteric orifice at fixed flow rates. With the bladder draining freely the absolute pressure is higher than the relative pressure by the extent of the intra-abdominal pressure.

If the lower end of the ureter was perfused at open operation the bladder could either be opened

and kept empty to give both a relative and an absolute pressure, which would be identical, or, alternatively, the volume of the bladder could be controlled by a urethral catheter and relative pressures obtained at varying volumes.

Table

Study Number	Patients' Initials	Age Y	Timing of Study M	Route of Access to Urinary Tract	Pressure (cm H ₂ O) at 10 ml./min.		Perfusion Fluid	Action Taken		
					Absolute	Relative				
1	D. M.	5	5	Before	Antegrade	11	...	Conray 325	Nil	
2	M. R.	5	9	valve	Antegrade	25	...	Urovison	Re-implant	
3	P. D.	2	wk	ablation	Nephrostogram	28	20	25% Hypaque	Too early	
Interval after valve ablation										
			Y	M						
4	M. L. (left)	3	5	8	Antegrade	11	...	Urovison	Nil	
5	R. B. (right)	9	7	—	3	Nephrostogram	11	...	35% Diodone	Re-implant
6	J. M.	3	—	1	6	Antegrade	13 11	11 9	35% Diodone Saline	Nil
7	D. F.	—	1	1	week	Nephrostogram	15	...	35% Diodone	Nil
8	D. G.	10	1	5	—	Antegrade	25	...	35% Diodone	Nil
9	A. P. (left)	2	2	—	11	Lower end	34	20	Saline	Re-implant
Interval after ureteric re-implant										
			Y	M						
10	A. P. (right)	2	2	—	10	Lower end	12	3	Saline	Nil
11	M. A.	3	9	1	2	Nephrostogram	13	...	35% Diodine	Nil
12	R. B. (right)	10	2	—	6	Antegrade	21	...	35% Diodone	Nil
13	R. B. (left)	10	5	—	10	Antegrade	24 18	19 13	35% Diodone Saline	Nil
14	P. S. (left)	9	1	3	4	Antegrade	43	37	35% Diodone	Nil
15	P. S. (left)	9	4	3	7	Nephrostogram	28 23	21 16	35% Diodone Saline	Nil
16	P. J.	5	1	3	—	Lower end	...	24	Saline	Re-implant
17	M. L. (right)	3	5	—	7	Antegrade	106	...	Urovison	Nil

Based on results in over 65 studies in both normal and abnormal ureters and on observations in animal studies we would expect a flow rate of 10 ml/min to produce no greater pressure rise in the kidney than 15 cm H₂O, and the pressure drop across the ureteric orifice (relative pressure) to be no greater than 10 cm H₂O.

Results

In our previous paper (Williams *et al.*, 1973) we gave details of the biochemical improvement or deterioration after valve ablation in these boys.

Intravenous urography showed that 70% of ureters and kidneys were grossly dilated before the valves were destroyed, whereas in the follow-up period only 45% remained dilated and this proportion was the same whether or not they showed vesico-ureteric reflux when they first presented.

Micturating cystograms in the pre-operative period showed reflux into one or both ureters in 44% of boys and the influence of reflux on the subsequent clinical course has also been discussed in our previous paper.

Amongst the 170 boys there were 70 ureters which remained grossly dilated in the follow-up period but showed no reflux, and it is these ureters which present the most difficult diagnostic and management problems.

Many of these dilated upper tracts had nephrostomy tubes inserted in the initial operative period, and in the ensuing weeks nephrostograms were performed. Early in the series these were done with hand-held syringes. Information was obtained concerning the size, distensibility and activity of the renal pelvis and ureter. The ease with which the contrast medium passed through into the bladder was not only variable from patient to patient, but in any one patient it was difficult to assess the adequacy of the orifice without knowledge of the pressure which was being applied from above. In some boys there was unequivocal hold-up in the lower ureter within 10 days of the operation on the valves, but after a further 2-3 weeks a nephrostogram showed contrast medium passing into the bladder despite residual gross dilatation and inertia. Others showed free flow into the bladder from the start and in these boys the nephrostomy tube could be clamped and removed with no ill effect. Others again appeared obstructed and remained so until re-implantation of the ureter was undertaken.

There is probably a wide range of degrees of obstruction between these clearer categories, and to detect these a number of boys were investigated by the urodynamic test which has been described.

17 studies were performed in 12 boys. Of these, 3 had bilateral studies and 2 had the same ureter examined on 2 separate occasions. The timing of these studies divided the boys into the following categories:

1. Boys studied at the time of the initial admission and before the valves were destroyed.
2. Boys studied at intervals of between 1 week and 5 years after valve ablation but whose ureters had not been re-implanted.
3. Boys who had a ureter studied at intervals after it had been re-implanted, with or without tapering.

The table indicates the findings in these 17 studies. Three boys were studied at the time of their initial admission. In the first child (study 1) there was free flow from an antegrade puncture down the ureter and into the bladder at a normal absolute pressure of 11 cm H₂O at 10 ml/min. The following day the valves were destroyed and this ureter and kidney have remained satisfactory since with no further attention.

The other 2 boys in this group had pressures over 25 cm H₂O at 10 ml/min. One has needed bilateral ureteric re-implants 4 months after valve ablation and the other, younger, boy is still under observation.

Six boys were studied at intervals of 1 week to 5 years after the valves were destroyed because of persistent ureteric dilatation. Two of these boys (studies 8 and 9) had high-pressure systems (absolute pressures of 25 and 34 cm H₂O). One boy has subsequently had the ureter re-implanted, and in the other boy the overall renal function is so poor, and the upper tracts so grossly dilated, that an ileal loop diversion would be the only appropriate treatment. This has been refused by the boy's parents. The other 4 boys had pressures within normal limits, but despite this 1 boy (studies 5 and 12) had a ureteric re-implantation and narrowing performed for a dilated upper tract and is discussed below.

These 4 boys with very dilated systems and normal pressures are typical of the group of boys

who after ablation of the valves have ureters which would be suspected of obstruction by standard investigations but have in reality overstretched and atonic systems.

In the last group there are 6 boys whose ureters had been re-implanted into the bladder at intervals of between 6 months and 3½ years previously, but had remained dilated on intravenous urography. Six of the 8 studies in these boys showed that the pressures were higher than normal on perfusion at 10 ml/min. Of these boys with high-pressure systems, 1 had a successful re-implantation (study 16). Another boy (studies 5 and 12) had the right ureter re-implanted and

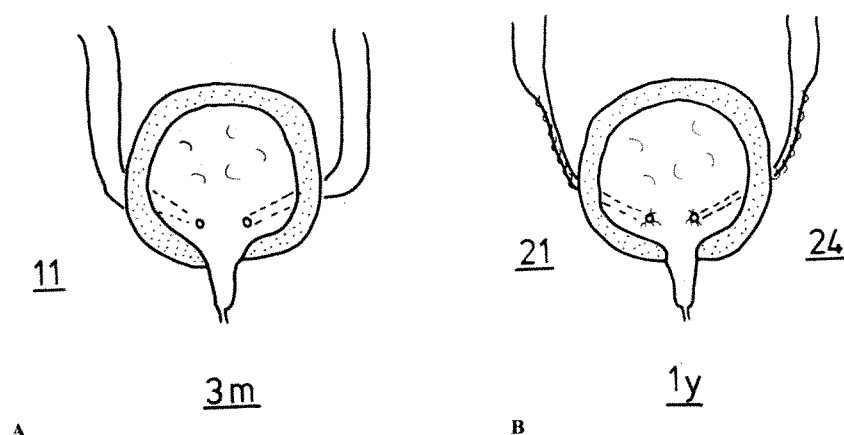


Fig. 2. 10-year-old boy whose right upper tract was studied via a nephrostomy tube 3 months after valve destruction **A**, and again at approximately 1 year **B**. In the interval both ureters had been tapered and re-implanted. Pressures in cm H₂O (absolute) at 10 ml/min.

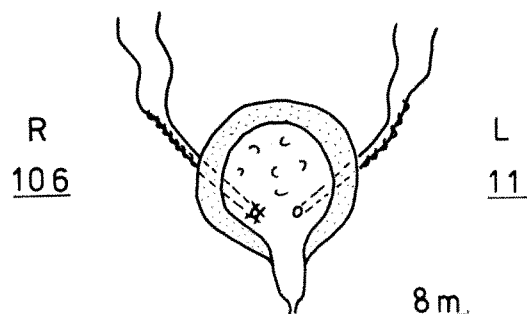


Fig. 3. 3½-year-old boy studied 7 months after bilateral tapering of the ureters but re-implantation on the right side only, and 8 months after the valve ablation. Pressures in cm H₂O (absolute) at 10 ml/min.

tapered despite a normal pressure, and when this ureter was again studied a year later the pressure was higher, suggesting that although the ureter was now narrower it had a higher overall resistance. The pressure was very similar to that in his opposite ureter after a similar re-implantation (study 13) (Fig. 2).

Another boy (studies 14 and 15) was found to have a high pressure in his left ureter on 2 occasions and is being observed carefully.

A 3½-year-old boy (studies 4 and 17) is of particular interest. He had operations on both his ureters 3 weeks after valve ablation; on the right side the ureter was tapered and re-implanted whilst on the left side the ureter was tapered outside the bladder but *not* re-implanted. Eight months later bilateral antegrade pyelograms and pressure studies were performed (Fig. 3).

The right, re-implanted, side showed a very high pressure on perfusion, whilst the left side was most satisfactory. At present this boy is being kept under frequent review. There seems little doubt that his right upper tract has a greater resistance than the left at 10 ml/min, but at the intrinsic flow rates of his kidney the ureter is coping so far.

One boy's ureter (study 11) perfused at low pressures and he is progressing well to date.

Studies 9 and 10 on a 2-year-old boy are of interest, as they illustrate the value of filling the bladder during the test. Nephrostograms after valve ablation showed gross dilatation (Fig. 4). Two weeks later the left nephrostomy tube was clamped and the urine drained well into the



Fig. 4. Nephrostograms in a 2-year-old boy, 11 days after insertion of the tubes, showing little contrast medium passing into the bladder.

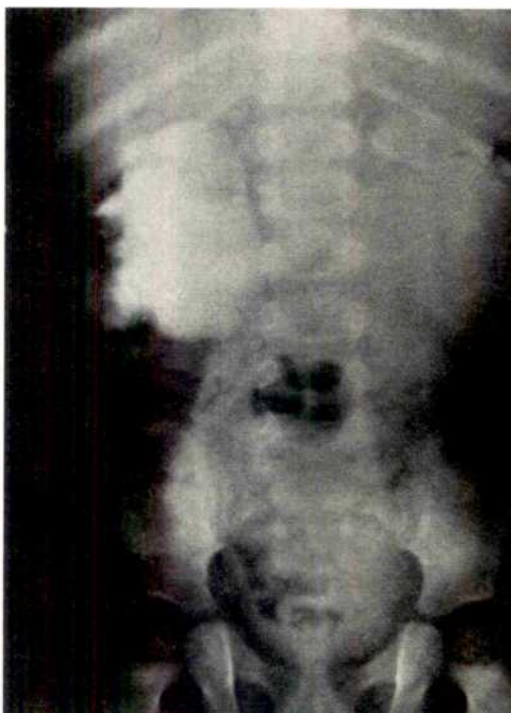


Fig. 5. Same boy as in Figure 4. Excretory urogram (80 min) 8 months after re-implantation of the right ureter. There is better concentration of the medium on the right side.

bladder. On the right the nephrostomy tube could not be clamped without leaking so a right re-implantation was performed a month after the operation on the valves. Ten months after this an intravenous urogram showed gross bilateral distension of the upper tracts with the left kidney showing worse concentration than the right (Fig. 5).

The lower ureters were then explored and perfusion studies with the bladder empty showed that the right (re-implanted) side was transporting well at a low pressure, whilst on the left side the relative pressure was raised to 20 cm H₂O (Fig. 6).

When the bladder was filled to 60 ml the relative pressure in the left ureter dropped to 9 cm H₂O suggesting that the resistance was lower with some fluid in the bladder, but on filling it to 170 ml the pressure again rose to higher levels (Fig. 6). The relative pressure in the right side also rose with bladder filling. To account for these changes the shape and length of the intramural ureter and ureteric orifice must be affected by the degree of distension of the bladder wall.

In studies 6, 13 and 15 the perfusion was with both 35% Diodone and saline. The pressure always dropped on converting to saline. The implications of this are discussed later.

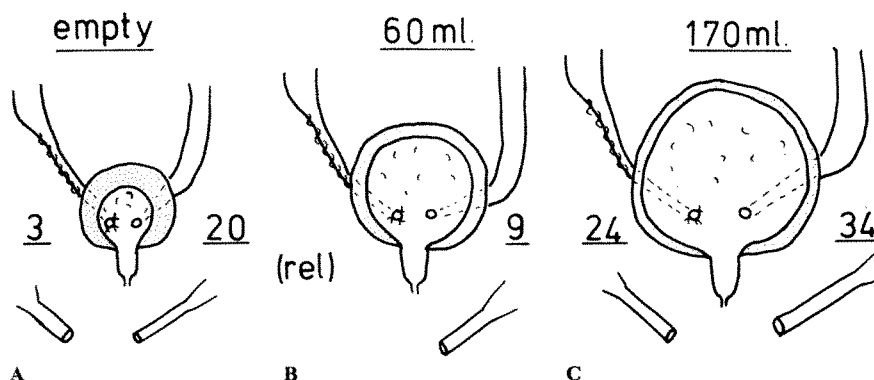


Fig. 6. Studies in the boy illustrated in Figures 4 and 5 approximately 11 months after valve destruction and 10 months after the right re-implantation and tapering. Pressures in cm H₂O (relative) at 10 ml/min. A, Bladder empty; B, 60 ml in bladder; C, 170 ml in bladder.

Discussion

All too often it is suggested or implied that because these grossly dilated ureters in boys with posterior urethral valves remain dilated in the postoperative period, in the absence of reflux, they must be obstructed at the ureterovesical junction. Sufficient spontaneous improvement was seen in our series and in others (Johnston and Kulatilake, 1972) for it to be clear that certainly not *all* such ureters are obstructed. The concept of gross dilatation being possible in the absence of obstruction is not easily accepted, particularly by urologists who do not regularly deal with abnormalities of the upper urinary tract in children. However, many megaureters in children and the typically dilated systems seen in the prune belly syndrome are obvious examples of gross dilatation which may be unassociated with any suggestion of obstruction.

With posterior urethral valves there is a continuous period of considerable obstruction to the outflow from the bladder. The higher-than-normal bladder pressure prevents the ureters emptying properly and this backpressure leads to overstretching and atony of the ureteric walls. Similar to the renal pelvis after pyeloplasty the extent to which there is a return to normality after relief of the obstruction is variable and unpredictable. Thus we should not be surprised that many of these ureters remain wide and atonic and we should not too readily conclude that there must be an obstruction at the level of the bladder wall.

We feel there is a wide range of degrees of obstruction at this level from severe to non-existent and that the key to selection for successful surgery is dependent on knowing this degree of obstruction.

Apart from the evidence supplied by the perfusion test, there are other pointers which suggest that obstruction is absent. A continuing improvement in the renal function, obvious structural improvement on serial intravenous urograms, and normal growth and health of these boys will suggest that all is well. In this series there were 13 boys who showed a remarkable resolution in ureteric dilatation during the follow-up period and it is difficult to imagine that their ureters were obstructed.

The excretory urogram provides much structural information but cannot be relied upon from a functional aspect either in respect to the kidneys or to the ureters. In the diagnosis of obstruction it can be misleading, as there are so many variable factors such as the nature and dose of the contrast medium, both absolute and related to the size of the child, the degree of dehydration,

the overall renal function, the ability of the kidneys to excrete the medium, whether there is an obligatory polyuria, the fullness of the bladder and finally the presence or absence of infection.

A retrograde catheterisation of the ureter or ascending ureterogram can give similarly confusing results as inevitably the degree of dilatation will depend on the force of injection of the medium. In the absence of effective peristalsis the rate of emptying of the ureter will depend on gravity and the excretory pressure from the kidney to propel the urine along.

The interpretation of nephrostograms can also be difficult: a hand-held syringe, for instance, will produce a high pressure easily and this will allow a deceptively easy passage of the medium into the bladder. The investigation becomes much more meaningful if the rate and pressure of the perfusion of the contrast medium is controlled.

So, it must be re-emphasised that in order to diagnose obstruction, information about pressures and flows must be obtained and it is here that we have found the perfusion test so valuable.

Most of the perfusion studies have been done after the retrospective series was closed so that we can provide no meaningful information about how many of our boys had obstructed ureters or whether they were helped by further operations.

In this series of 12 boys who were studied because of persistent ureteric dilatation the results suggest that the majority of non re-implanted ureters are not obstructed. The perfusion test, however, picked out 2 boys whose ureters did need re-implanting (studies 2 and 9) and these were successfully performed.

Many of the ureters which had been re-implanted showed high pressures and underline the hazards of re-implanting a dilated ureter into a thick walled bladder.

The overall results emphasise the wide range of degrees of ureteric resistance which may be present in association with ureteric dilatation from normal to high; a range which is undetectable from, and correlates poorly with, the urographic appearances.

Two of the 3 boys studied before the valves had been destroyed showed high pressures and it is certainly our clinical impression that when the bladder is first decompressed the thick bladder muscle clamps down on the ureter. We feel that this may be one reason why urethral catheter drainage is often less effective than drainage via nephrostomy tubes.

The part the bladder wall plays in allowing good ureteric drainage is not clear. Study 9 suggests that the ureter may drain best when the bladder is partially full and this somewhat bizarre behaviour would go a long way to explain the apparent hold up one sees at the lower ureter in the post-voiding films at excretion urography.

The remaining hypertonicity of the bladder after valve ablation may be a contributing factor in persistent ureteric dilatation and poor emptying, but *this must not be confused with a mechanical obstruction in the lower ureter*. Not uncommonly a ureter which was refluxing before valve ablation stops afterwards and appears obstructed on an excretory urogram but we suspect that this phenomenon is due more to a high pressure within the bladder than to the appearance of obstruction in the lower ureter.

The intrinsic flow rate from the kidney throughout the perfusion is a potential source of error. This has been calculated in some boys with nephrostomy tubes and has never amounted to more than 5% of the total flow rate during the test and can be lessened by having the boy well dehydrated.

All contrast media have higher viscosities than saline and experiments with perfusions in fixed and variable diameter objects suggest that pressures should vary by a factor of 1.5-3 depending on the media. In practice, however, we have not found such variations (studies 6, 13 and 15). This may in part be due to dilution of the media by urine.

Interpretation of these studies is not always easy, but we feel that if there is a minimal pressure rise at this high flow rate there can be no mechanical obstruction. Higher pressures are suggestive of obstruction, but our emphasis has always been on trying to exclude obstruction because it is not easy to decide what levels are normal in various sizes of children. Only by collecting data in large numbers of normal and abnormal children of all ages will we be able to answer this.

However, our experience so far suggests that normal ureters of almost any size can conduct such high flow rates as 10 ml/min with minimal pressure rises.

Repeated studies should help to elucidate the natural history of these ureters, but this is not always practical and so far no fixed pattern of behaviour has emerged. We have been surprised and relieved on several occasions to find ureters in which we suspected obstruction draining freely to the bladder at low pressures and we have saved these boys operations by leaving them alone.

We feel that it is important to diagnose obstruction early to avoid slow but inevitable deterioration in renal function. Without objective evidence of obstruction it is tempting to taper and re-implant all these dilated ureters, but our results and those of others show that this can be a hazardous procedure in these boys, leading either to unquestionable obstruction or even reflux.

We are now inclined to offer further operations to those boys with proven obstruction, particularly in the presence of paraureteral saccules, those with persistent urinary tract infections, and those with deteriorating renal function, particularly after a period of initial improvement. If the renal function is poor, the ureters atonic and the bladder function unsatisfactory, we are inclined to perform a high ileal loop diversion of urine.

We are not impressed by our results of total reconstructive surgery in the young child as advocated by Hendren (1972), but would reserve this for the older boy with good renal function but with gross stasis of the upper tract.

Summary

A main problem in the management of boys after ablation of posterior urethral valves is the diagnosis of ureteric obstruction.

An accurate diagnosis of obstruction is essential if unnecessary operations are to be avoided and intravenous and retrograde urography in this respect have their limitations.

Perfusion studies as discussed here have proved valuable and the results of 17 studies in 12 boys illustrate that there is a wide variation in degrees of obstruction which often correlate poorly with urographic assessment.

These studies have helped to plan a more logical approach to ureteric surgery in these boys.

All the patients in this study were under the care of Mr David Innes Williams and I am grateful to him for allowing me to study them, and for all the encouragement he has given me. Thanks are also due to the Hospital for Sick Children, London, and the St Peter's Group of Hospitals, London, for permission to reproduce the radiographs.

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Ureterocele Calculi

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It has long been recognised that ureteroceles often contain calculi. Lowsley and Kirwin (1956) gave the incidence as 4%. Aas (1960) found calculi to be present in 39%. Thompson and Kelalis (1964) reported calculi to be present in 15% of their cases.

Freyer in 1897 first suggested that calculi might be the primary cause of the ureterocele. Other authors have supported this hypothesis including Caulk (1913) and Raper (1958) suggested that a stone lying in the lower end of the ureter led to the dilatation. Of recent authors on ureteroceles Sherwood and Stevenson (1969) support Raper's view that the calculus may have impacted in a normal ureteric orifice.

We report 3 cases of ureterocele calculi of such a size that they could not have come down the ureter. They were laminated stones throughout and had obviously formed in the ureterocele.

The other point of interest about these cases is the manner in which such ureteroceles mimic bladder tumours, not only in their symptomatology but also on cystoscopic appearance.

Sherwood and Stevenson (1969) discussing "ureteroceles in disguise" warn of bladder tumours mimicking ureteroceles. It is our opinion that the converse is much more likely to occur.

Case 1. A 66-year-old woman complained that for 3 years she had had recurrent attacks of dysuria and frequency. There were no abnormal findings on examination. Her urine contained more than 500 leucocytes per c.mm. and was infected with *proteus*. The abdominal X-ray showed 2 stones to be present in the bladder region (Fig. 1, A). I.V.P. showed the stones to be in ureteroceles (Fig. 1, B). The right ureter was somewhat dilated and there was a right renal calculus.

At cystoscopy, a large polypoid tumour was visualised and the original cystoscopist considered this to be a bladder tumour and a biopsy was performed. This showed the appearance of cystitis glandularis. The calculus was palpable bimanually.

Cystotomy was performed and the ureteroceles were confirmed (Fig. 1, C). The one on the left contained a calculus 3 cm in diameter. On the right a small ureterocele contained a 0.6 cm stone. Both ureteroceles were excised (Fig. 4). The patient made an uneventful recovery. The urine became sterile and free of pus cells.

Case 2. A 44-year-old man was admitted as an emergency with profuse haematuria. For 2 months he had had severe urgency and strangury and in the week before admission suffered penile pain.

His urine was heavily blood-stained but not infected. The abdominal X-ray showed a calculus in the bladder region (Fig. 2, A). The I.V.P. showed it to be in a ureterocele (Fig. 2, B). At cystoscopy the calculus was found to be impacted in the orifice of the ureterocele and was released by diathermy incision of the neck. The calculus was crushed with a lithotrite and the ureterocele collapsed on being incised. The patient's symptoms were completely relieved and I.V.P. 3 months later showed no recurrence.

Case 3. A 59-year-old woman was seen complaining of painless haematuria. She had had several similar episodes and rectal examination showed a mass to be palpable in the right side of the pelvis. The urine was infected with *E. coli*.

The I.V.P. showed the typical appearance of a ureterocele calculus on the right side (Fig. 3); not the bladder tumour suspected from the patient's history and examination findings.

Cystotomy and excision of the ureterocele was followed by relief of her symptoms. The calculus was a laminated stone 2.7 cm in diameter.

Comment

The calculi in these cases measured 3 cm, 2.7 cm and approx. 2 cm. They were composed of a mixture of calcium oxalate and phosphate. Two appeared laminated on section. It would seem that such stones must have formed in the ureteroceles.

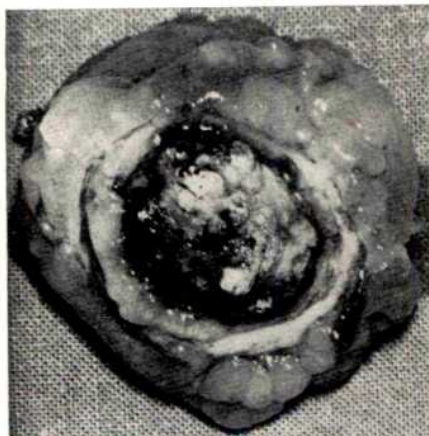
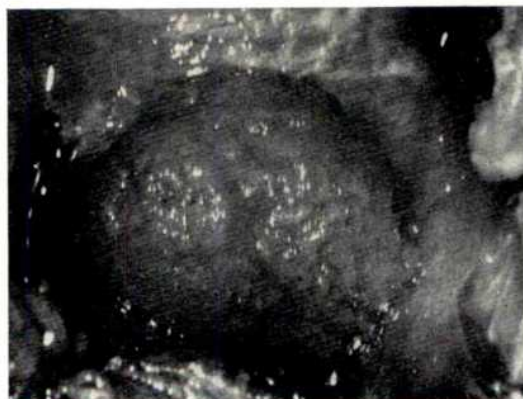
**A****B****C****D**

Fig. 1. Case 1. **A**, Plain X-ray showing calculi in right kidney and bladder regions. **B**, I.V.P. showing calculi in ureteroceles. **C**, Appearance at operation. **D** Specimen showing calculus.

The supporters of the acquired theory of ureterocele formation stress the frequency of calculus formation in the upper urinary tract in these patients. Asa (1960) reported 13 ureteroceles containing calculi and 5 of these had concurrent ipsilateral stones. In no case was an isolated calculus found on the side opposite to the ureterocele.

As obstruction and dilatation of the ureter is a common finding in ureterocele it seems more likely that these calculi in the upper urinary tract are a result of the stasis and infection which is found in most cases (Kelalis, 1967).

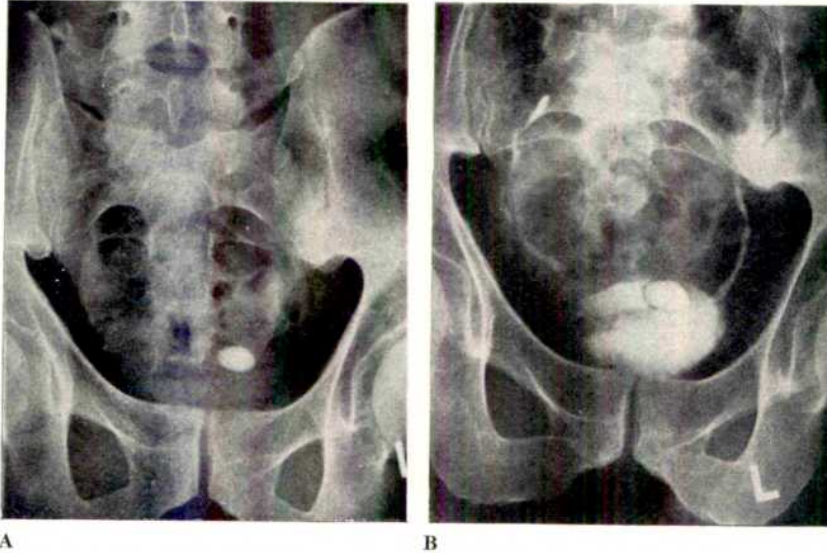


Fig. 2. Case 2. A, Plain X-ray showing calculus in bladder region. B, I.V.P. showing calculus in left ureterocele.

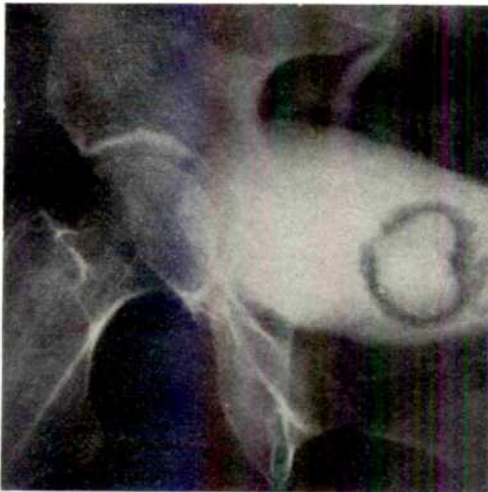


Fig. 3. Case 3. I.V.P. showing calculus in right ureterocele.

In each of these 3 patients tumour was considered as a possibility. The history of Case 3 was very suggestive of a tumour and the presentation of Case 2 with profuse haematuria is unusual for a ureterocele. In Case 1 an experienced surgeon considered the cystoscopic appearance to be typical of neoplasm.

The characteristic cobra head appearance of the lower ureter on the pyelogram is diagnostic,

and when the opacity on the pyelogram is compared to the size of the calculus on plain X-ray it appears larger due to the pool of radio-opaque urine surrounding the stone in the ureterocele.

The cystoscopic appearance of the ureterocele may be strikingly similar to a neoplasm particularly if there is accompanying cystitis. Ureteroceles containing large calculi do not empty while being observed. Kelalis (1967) stressed that ureterocele may be confused with a vesical neoplasm on cystoscopy and other authors have found that rectal palpation of a ureterocele calculus has led to erroneous diagnosis (Hopewell, 1952).

The treatment of such cases should be either incision transurethrally or excision by a trans-vesical approach as recommended by Dodson (1970), Kickham (1944) and others. Reflux may occur after operation in these cases but it is the opinion of many that it is rarely a problem (Raper, 1958). Operations to prevent reflux after surgical repair of ureterocele as described by Hutch and Chisholm (1966) seem unnecessary.

Summary

The clinical and radiographic findings in 3 cases of calculi in ureteroceles are described.

We would like to thank Mr Hugh Anderson and Mr K. Wilkinson for their help in preparing this paper.

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Estimation of Residual Urine Volume with ¹³¹I-Hippuran

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Failure to empty the bladder completely may affect the ability of patients to eliminate urinary infection (O'Grady and Cattell, 1966); and there is clinical evidence that it makes bacterial cystitis more difficult to treat (Shand *et al.*, 1970). Measurement of residual urine is thus, increasingly, a part of the management of patients with recurrent bacterial cystitis.

The residual volume is less than 1 ml in normal subjects (Hinman and Cox, 1967; Shand *et al.* 1970), and a satisfactory technique for measuring it must be accurate within this range if deviations from normal are to be detected. An estimation which depends on surface counting of ¹³¹I-Hippuran in the bladder before and after micturition (Shand *et al.*, 1968) is free of some of the drawbacks of previous methods, but still has possible sources of error. Among these, 2 may be significant. First, the assumption that no ¹³¹I-Hippuran enters the bladder between voiding and external counting of the residual urine. Secondly, the method of measuring background activity—that arising from sources other than the Hippuran in the bladder. It is necessary to subtract this background reading from the radiation present in the bladder area after voiding to assess the radiation due to the residue.

In this paper these two sources of error are examined; and, as the first appears to make a considerable, but predictable, contribution, a modification of the technique is suggested which eliminates the inaccuracy it introduces.

Materials and Methods

Indicators and Instrumentation

¹³¹I-sodium iodohippurate (¹³¹I-Hippuran) containing 1% benzyl alcohol, and ¹³¹I-Human Serum Albumin (RIHSA) were obtained from the Radio-Chemical Centre, Amersham.

The radiation dose from 10 μ Ci ¹³¹I-Hippuran after 3 hours' retention in the bladder is 190 mrem to the thyroid gland blocked with iodine, and 78 mrem to the bladder (Henk *et al.*, 1967). This is well within the prescribed limits of the International Committee for Radiation Practices, 1965.

The detector was coupled to a power supply, a pulse height analyser and a digital scaler. The scintillation counter consisted of a 1 inch diameter $\times$ 1 inch sodium iodide crystal and photo-multiplier with a collimator 5 cm deep which had an internal diameter of 5 cm. A continuous record was made on a Leeds and Northrup "Speedomax W" multipoint recorder.

Residual Urine Estimation

200 mg of potassium perchlorate was given on the evening preceding the examination. After emptying the bladder each subject was given 10 μ Ci of ¹³¹I-Hippuran intravenously, and the opportunity was taken to make a renogram tracing. 1½ to 3 hours later the activity in the bladder area was measured by external counting, before and shortly after voiding. The background activity was measured at the umbilicus with the patient in the supine position, and, in certain cases, measurements of background activity were also made at the umbilicus with the patient in the sitting position, and over the thigh.

The residual urine was calculated from the formula

$$R = \frac{(C2 - B)V}{C1 - C2},$$

where R = residual urine

$C1$ = activity over the bladder before voiding

$C2$ = activity over the bladder after voiding

B = background

V = volume voided.

For bladder counting, the collimator was centred 2.5 cm above the pubic symphysis. The thigh count was obtained with the counter horizontal over the lateral surface of the thigh with the patient standing. Counts were taken for not less than 100 seconds.

Experimental Design

The assumption that no significant amount of ^{131}I -Hippuran enters the bladder between voiding and re-measurement over the bladder was tested by measuring:

1. The activity over the bladder after voiding, making a continuous record for 30 minutes (8 patients).
2. The activity over the bladder at 5-minute intervals for 30 minutes after voiding (8 patients).
3. The bladder and background activities immediately after voiding and again 30 minutes later, calculating the apparent residual urine volume for each pair of readings (59 patients).
4. The activity of the urine passed in the hours following the test (4 patients).

The suitability of the umbilicus as a background reference point was assessed in 9 patients by comparing the activity over the bladder 24 hours after an IV injection of radio-iodinated human serum albumin (RIHSA) with the radiation at the umbilicus with the patient supine.

The activity at the umbilicus (erect) after Hippuran was compared with that over the thigh in 45 subjects, and the activities at all the 3 reference sites [umbilicus (erect), umbilicus (supine), and thigh] were compared in a further 20 subjects.

Results

Secretion of Hippuran after the Test Period

The activity in the bladder area rose steadily with time after voiding in all 8 patients in whom it was continuously monitored. This effect was seen when voiding occurred 100 minutes after injection and it was also present 180 minutes after injection. Figure 1 displays a tracing obtained from a subject who held his urine for 180 minutes after the injection of ^{131}I -Hippuran. The upper trace was obtained from the bladder area and shows a linear rise from 4.0 to 5.2 counts per second in 15 minutes.

The rise in activity over the bladder area appears linear with time within the period of investigation in all 8 cases. Its approximate linearity can be expressed statistically by calculating the correlation coefficient, r , for each case. For this purpose the instrumental time constant was 10 seconds, and the activity was read off the trace at 100-second intervals. The correlation coefficients have been tabulated in Table I, together with the mean rise in residual urine in each 5 minutes and the true residual urine, calculated by extrapolating back to zero time. It can be seen that the rise in apparent residual urine varies in different subjects from 0.4 ml to 2.5 ml per 5-minute period. The correlation coefficient determined by this method is high, having a mean figure of 0.980.

Individual counts of activity in the bladder area measured at 5-minute intervals for 30 minutes after voiding in 8 subjects, also showed a consistent rise (Fig. 2). Once again the rise in residual urine appeared linear with time.

In 59 patients, readings of the bladder and background activities were obtained soon after voiding and again 30 minutes later. From these figures the apparent residual urine at these 2 times was calculated. In each case there was a significant increase in residual urine during the 30-minute interval. The calculated residual urine increased at a mean rate of 0.20 ml/min, but

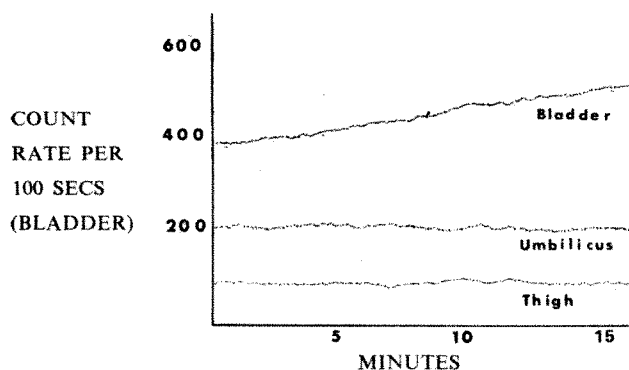


Fig. 1. The activity over the bladder, at the umbilicus, at the thigh, immediately after voiding. Records taken simultaneously from a subject with normal renal function who voided 180 minutes after an injection of ^{131}I -Hippuran. The three traces are not on the same scale. The linear rise in count rate over the bladder area is clearly demonstrated.

Table I

Eight Subjects; Residual Urine calculated from Readings of B and C2 taken at 5-minute Intervals after Voiding

Patient	Rise in Apparent Residual Urine (ml/5 min)	Correlation Coefficient (<i>r</i>)	True Residual Urine (ml)
1	2.5	0.995	14.2
2	1.5	0.907	4.1
3	1.0	0.988	0.26
4	1.65	0.994	nil
5	0.4	0.996	3.4
6	0.5	0.966	4.0
7	0.55	0.987	2.3
8	1.8	0.980	1.08

with a wide variation (2SD = 0.22 ml/min). The largest increase was 0.47 ml/min and the smallest 0.01 ml/min.

The continuing excretion of Hippuran 180 minutes after the initial injection was confirmed by measuring the activity in the urine passed after this time. Four patients, all with normal renal function and residual urine volumes of less than 2 ml, co-operated in this study. The urine passed in the 180 minutes after the test had been completed was collected. The activity in these samples, expressed as a percentage of the original dose, is displayed in Table II. It can be seen that 3.9 to

8.0% of the original dose is secreted in the urine during the period 180 to 360 minutes after the initial injection.

The Umbilicus as a Background Reference Point

The activity due to RIHSA 24 hours after its injection was measured at the umbilicus (supine) and over the bladder in 9 subjects. The readings obtained were almost identical at the 2 sites. The difference was never greater than 5%. It ranged from 1.1 to 4.8% with a mean of 4.4%.

The ratio between the activities at the 3 background sites can be compared after Hippuran. The thigh gave a reading which, in 65 subjects, was never greater than that taken at the umbilicus with the patient in the erect position. It was usually less (mean $20.7\% \pm 31.5 = 2\text{SD}$. $N = 65$).

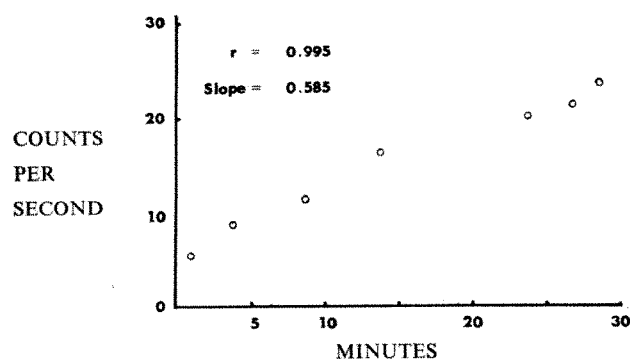


Fig. 2. The activity over the bladder area measured at approximately 5-minute intervals after voiding (200 second counts. Patient with normal renal function).

Table II

The Activity in the Urine passed 180-360 minutes after an Injection of ^{131}I -Hippuran, expressed as a percentage of the original dose

Patient Number	Percentage of Dose in Urine passed 180-360 minutes after Injection
1	8.0
2	3.9
3	3.9
4	7.6

The activity measured at the umbilicus with the patient sitting was almost always greater than that when the patient was supine, especially in patients with hydronephrosis or mobile kidneys.

It is concluded that the activity measured at the umbilicus with the patient supine gives the best approximation to the bladder background activity.

Discussion

The principle of measuring residual urine using an indicator which enters the bladder in the urine by renal excretion was introduced by Cotran and Kass (1958). Their method had the

overriding advantage that catheterisation, with its attendant risks of infection, was avoided, but it suffered from the disadvantage that the indicator, phenolsulphonphthalein, was slowly cleared from the blood, and that excretion into the bladder was still continuing at a time when the patient had to void, especially if renal function were poor.

^{131}I -Hippuran has the advantage that it is rapidly excreted by the renal tubules, and it has been stated that almost all of it has been excreted in the urine within 2 hours of injection. The external counting method was considered accurate even in renal failure (Mulrow *et al.*, 1961). Shand and his colleagues (1968) accept that 90 minutes between injection and voiding should be satisfactory when renal function is good; and that 130 minutes is adequate in moderate renal failure. Our findings conflict with this view. A period of at least 3 minutes is likely to elapse between voiding and the mid-point of external counting. In this time ^{131}I -Hippuran enters the bladder in an amount sufficient to add 0.03–1.41 ml to the residual urine in calculation.

Hinman and Cox (1967) have shown the average residual urine to be 0.53 ml (0.09–2.34) in young men, and similar figures (0.14–0.84 ml) have been found by Shand *et al.* (1970). An error of up to 1.4 ml seems to be too large in relation to a normal value of less than 1.0 ml to be acceptable.

It has been suggested by Rosenthal (1963) that a corrective calculation could be employed. Our finding that the rise in activity over the bladder area appears linear with time confirms that the residual urine volume immediately after voiding can be determined if readings of the activity over the bladder and of the background are taken at a short, measured, time after voiding and again 30 minutes later.

The apparent residual urine can be calculated for each pair of readings. The rate of increase can be noted and the true residual urine volume can thus be determined.

The use of such a corrective calculation has a number of advantages, in addition to the obvious one of being more accurate. First, it is no longer necessary for the first count to be made immediately after voiding so long as the time is noted. Thus, there is no need for patient or staff to feel hurried. We have found this an advantage in a department where several residual urine estimations are to be made on the same morning, and, though it is hard to prove, we feel that micturition is more likely to be normal if the need for hurry is eliminated. Secondly, the statistical error of a radioisotope measurement decreases as the length of the counting period is increased. We routinely use a 400-second count over the bladder, and this imposes an obligatory delay of 200 seconds between the beginning and mid-points of the count, which must be added to the time allowed for positioning. The rise in activity over the bladder area in the 30 minutes after voiding appears linear when examined 90 minutes after the injection of Hippuran. If a correcting calculation is made it is unnecessary to wait longer than 90 minutes before voiding. The inaccuracy introduced by continued excretion of ^{131}I -Hippuran can be reduced if a longer period is allowed to elapse after injection. However, this is not a satisfactory solution as it makes the investigation unacceptably long, and as excretion of Hippuran from healthy kidneys, though less at 180 minutes than at 90 minutes, is still sufficient to introduce an unpredictable inaccuracy.

It appears that the upper limit for residual urine in normal subjects is 1 ml (Hinman and Cox, 1967). The application of the correction reduced the apparent residual urine (calculated from the figures obtained 300 seconds after voiding) from above 1 ml to below 1 ml in 10 of our 69 subjects.

An assessment of the background radiation in the bladder region (*B*) is crucial to the calculation of residual urine, as it is not small in comparison to the bladder count after voiding (*C*₂). The activity over the precordium has been used to provide a tissue background (Mulrow *et al.*, 1961; Lindbjerg and Brandt, 1964) but it appears to give too low a figure (Rosenthal, 1963; Shand *et al.*, 1968) and would give a falsely high reading for the residual urine volume. Shand and his colleagues (1968) have employed the umbilical count as a tissue background, getting readings within 5% of the count over the bladder in patients with end stage renal failure who produced only small amounts of urine.

In our hands the count over the umbilicus appeared to be too high when the patient was sitting. In 8 of 59 subjects it was greater than the bladder count, so that a negative value for residual urine volume was obtained. This occurred particularly in patients who had hydronephrosis and in patients whose kidneys were mobile so that they fell into the field of view of the collimator in the erect position. Negative values for residual urine volume were not obtained when the background reading was taken from the umbilicus with the patient supine.

Radio-iodinated human serum albumin penetrates the extravascular space, and 24 hours after injection is uniformly distributed through it (Lawson, 1962). It was used to compare the tissue background radiation in the bladder area with that at the umbilicus because it was being given routinely to patients undergoing CABBS renography, despite the realisation that the distribution of Hippuran and RIHSA might not be identical. Hippuran and RIHSA are both predominantly extracellular at the times that they were counted. We have shown, in 9 patients, that the activity over the bladder area 24 hours after RIHSA approximates to the activity measured over the umbilicus with the patient supine. This suggests that the extracellular tissue volumes under the field of the collimator are similar at the 2 sites. These findings are in agreement with Shand and his colleagues (1968).

As the umbilical count approximates to the bladder count, and as the thigh count tends to be lower than the umbilical count, we consider that the umbilical count provides a better approximation to the background which would be obtained from the bladder area.

The collimator used in our laboratory had a wider field of view than that used by Shand and his colleagues (1968). If the umbilicus count is to be compared with the bladder count, the crystals and collimators used at the 2 sites must be similar. A collimator giving a narrow field of view at the umbilicus would reduce the chance of "cross-talk" from the kidneys, but this advantage is offset by the possibility that a narrow collimator would not include the whole of the bladder area.

Summary

The use of ^{131}I -Hippuran for the determination of the residual urine volume has been studied. It has been shown that a significant error is introduced into residual urine calculation by the small amounts of ^{131}I -Hippuran which continue to be excreted in the urine for some hours after intravenous injection, even when renal function is good.

The rise in activity over the bladder area appears to be linear with time in individual patients, but the slope is unpredictable. True residual urine volume can be calculated if readings of the activity in the bladder area and at the background site are taken at a short, measured interval after voiding, and again 30 minutes later. The use of such a corrective calculation has a number of practical advantages, and makes the determination more accurate. The activity measured over the umbilicus with the patient supine appears to give a satisfactory tissue background reading.

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Transsacral Cystectomy¹

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The transsacral approach to pelvic surgery was introduced more than 85 years ago by Kraske (1887), and Goetze (1931) repopularised this approach to rectal surgery. Thiermann adapted the technique for transection of pelvic nerves in interstitial cystitis (1949) as well as radical prostatectomy and simple cystectomy (1952). Boeminghaus (1951) advocated transsacral cystectomy, while Campbell and MacGregor (1969) reported successful prostatic enucleation utilising the Fabre incision (1953). Kishev (1960) modified the transsacral approach for radical prostatectomy, and other authors have stressed the relatively low morbidity associated with the transsacral approach. Based upon these previous experiences, the transsacral approach has been utilised in 19 patients undergoing simple cystectomy for carcinoma of the urinary bladder as a second stage procedure after urinary diversion.

Indications

We have found several advantages in the transsacral route for cystectomy. First, the approach may be less difficult than classical anterior cystectomy in patients who have undergone multiple previous abdominal operations. Second, previous transabdominal urinary diversion, particularly by ileal conduit, may offer anatomical limitations to anterior dissection and exposure. Third, previous radiation therapy to the lower abdomen and pelvis may produce extensive anterior fibrosis and induration, while the posterior approach remains relatively free. Fourth, in instances of advanced vesical malignancy only palliative cystectomy may be required which is easily achieved through the posterior transsacral approach. Fifth, cystectomy by the transsacral route appears to involve relatively low morbidity and may be advantageous in poor risk patients.

Operative Technique

Position of the Patient

The patient is placed prone with the crest of the ilia below the second break of the table, legs suspended from stirrups and thighs abducted. Buttocks and genitalia extend approximately 4 to 5 inches beyond the lower edge of the table which is then flexed to 30 or 40 degrees (Fig. 1, A). Similar positioning may be achieved on a standard operating table without use of stirrups (Fig. 1, B).

The Approach

A reverse C-shaped incision is made, the upper transverse portion at the level of S4-S5 and the lower transverse segment between the ischial tuberosities with the vertical component over the right ischiorectal fossa (Fig. 2). Subcutaneous tissues are reflected, exposing the periosteum of the sacrum and the gluteus maximus muscle. The periosteum at S4-S5 is incised, reflected with the periosteal elevator, and the sacrum is then transected with a broad osteotome. The gluteus maximus muscle is incised and fibrous attachments are divided. The distal sacral artery is identified and ligated. The distal and left lateral attachments of the sacral segment are left intact and the right ischiorectal fossa is developed by blunt and sharp dissection to expose the levator ani which

¹ Read at the 28th Annual Meeting of the British Association of Urological Surgeons in Newcastle upon Tyne, July 1972.

is incised vertically in its mid-portion. The plane between the prostate and rectum may be entered by digital dissection, though in cases of advanced carcinoma of the bladder, particularly with

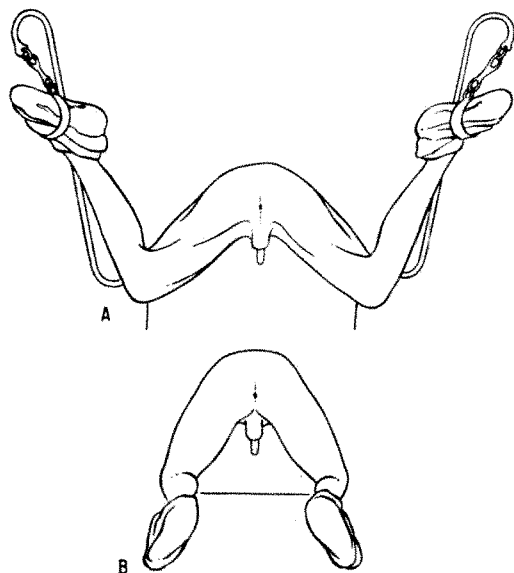


Fig. 1. A, The standard or "sky-diver" position of patient for transsacral cystectomy, utilising stirrups for suspension of the legs. B, Alternative position on a standard operating table.

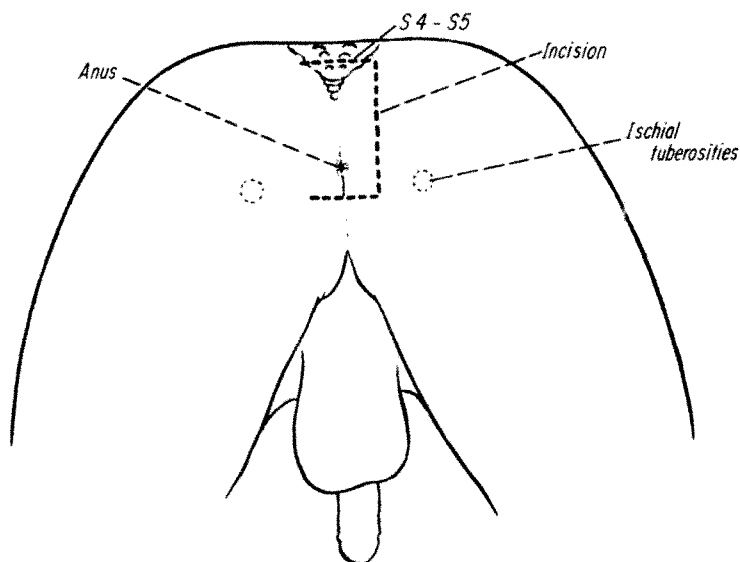


Fig. 2. Localisation of the reverse C-shaped incision for transsacral cystectomy.

previous radiation therapy, the cleavage plane of Denonvilliers' fascia may be obliterated and sharp dissection may be required.

Caudally, the apex of the prostate may be identified and dissection may be carried down upon the membranous and bulbous portions of the urethra distal to the prostate. The corpus spongiosum

may cause some bleeding during this phase of dissection. With traction clamps on the lower flap of the incision and an examining finger in the rectum, the membranous urethra is identified and transected, permitting mobilisation of the prostate from the rectal wall. The rectal ampulla is then mobilised by blunt and sharp dissection, retracting it laterally to the left to expose the

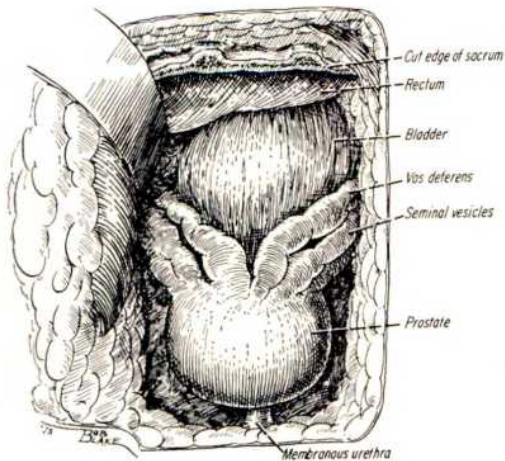


Fig. 3. Exposure of the posterior aspect of the bladder, vasa, ampullae, seminal vesicles and prostate following mobilisation and displacement of the rectum.

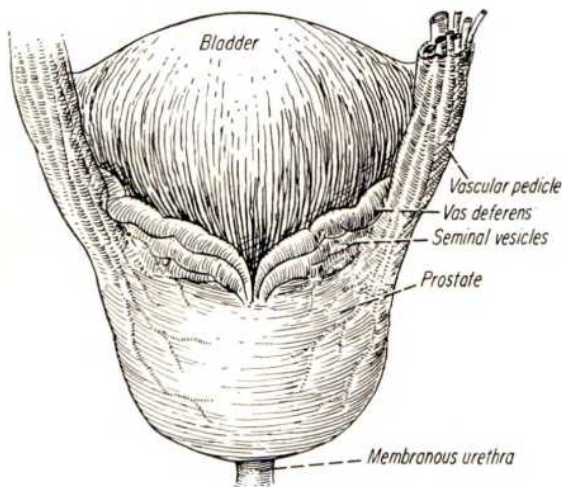


Fig. 4. Following dissection of endopelvic fascia, the vascular pedicles are secured, the membranous urethra is transected, anterolateral mobilisation is effected and the *en bloc* specimen consists of the entire bladder, prostate and seminal vesicles.

fascia investing the seminal vesicles and posterior bladder wall. The most tedious portion of the rectal reflection is at the junction of prostate with seminal vesicles, but once the rectum has been mobilised at this point, it can be reflected laterally to the left *en bloc* with the sacral flap (Fig. 3). The endopelvic fascia may then be incised lateral to the base of the bladder, giving access to the vascular pedicles of bladder (Fig. 4).

Preliminary Vesicolysis

Early experience with transsacral cystectomy indicated that the most difficult portion of the transsacral procedure was the subsequent mobilisation and delivery of the anterior and superior

portions of the bladder, particularly at the point of peritoneal attachment. Accordingly, anterior mobilisation and extraperitonealisation of the bladder were effected in the latter 14 patients in this series at the time of the urinary diversions greatly facilitating subsequent transsacral dissection and delivery of bladder and prostate. In the manoeuvres of anterior mobilisation and extraperitonealisation—cystolysis—a patch of peritoneum is circumscribed at the dome of the bladder, the anterior bladder is thoroughly mobilised and the bladder is displaced below the peritoneal reflection. The pelvic peritoneum may then be closed over this, or the anterior wall of the redundant sigmoid may be sutured into the peritoneal defect, effectively extraperitonealising the urinary bladder. When subsequent transsacral cystectomy is planned for 1 to 3 weeks later both hypogastric arteries may be ligated at the time of cystolysis, providing the benefits of additional haemostasis at the time of transsacral cystectomy.

When this preliminary cystolysis has been done, the anterior dissection and mobilisation are greatly simplified. The apex of the prostate is retracted posteriorly, giving access to the pubo-prostatic ligaments which are transected. Blunt dissection is then carried along the posterior aspect of the pubis, freeing the prostate and bladder from its lower attachments. The lateral attachments are then palpated, digitally undermined, dissected, clamped and divided. Since the major blood supply of bladder and prostate enter through these lateral pedicles, heavy transfixion suture ligatures are employed. Once these attachments have been divided, the entire specimen consisting of bladder, prostate and seminal vesicles may be removed. The residual cavity, isolated by the previous cystolysis procedure, is drained by suction (Hemovac) or multiple Penrose drains and the rectum is allowed to fall back into its normal position, virtually obliterating the cavity. Closure is effected by replacement and approximation of the distal sacral segment utilising interrupted heavy chromic catgut sutures. The transected edges of the gluteus maximus are similarly reapproximated, subcutaneous tissues are closed loosely with absorbable sutures, and skin edges are closed with choice of suture materials, drains being brought out through the vertical portion of the incision or inferiorly through the transverse portion.

Results

Staged surgery for palliation or potential cure of carcinoma of the urinary bladder was selected for 19 patients. The decision to stage the procedure—exploration with ileal conduit urinary diversion as the first stage, followed after an interval of about 2 weeks by cystectomy—was made on the basis of the reduction of morbidity and mortality by such staging, as reported by Grimes *et al.* (1972). Cystectomy by the transsacral approach at the second stage was selected in these cases because of the various advantages cited previously. In all 19 patients, operated upon consecutively, transsacral cystectomy was accomplished within 2 weeks after ileal conduit urinary diversion, some patients having undergone cystolysis as described. There was no operative or postoperative mortality, and morbidity in these 19 patients did not exceed that noted in a comparable group of patients undergoing staged diversion followed by secondary anterior cystectomy. The 19 patients can be categorised in 3 groups.

Group 1. Five patients with advanced carcinoma of the urinary bladder, tumour extending beyond the confines of the bladder wall, had preliminary irradiation and ileal conduit urinary diversion without attempt at cystolysis. Transsacral cystectomy was accomplished with difficulty in this group, predominantly because of adhesions of the bladder and tumour to the peritoneum and the anterior abdominal wall. Total extirpation of malignancy could not be effected in any of these 5 patients, and in 2 patients recurrent tumour was manifested in the perineum at 2 months and 6 months postoperatively. Wound healing was satisfactory in 2 patients and was markedly delayed in 3.

Group 2. Eight patients with extensive bladder carcinoma involving the pelvis extravesically had undergone various and repeated efforts at control of malignancy, including multiple transurethral

resections, radiation therapy and segmental bladder resections. Ileal conduit urinary diversion was accompanied by extensive cystolysis and extraperitonealisation of the bladder and a small segment of peritoneum. Hypogastric artery ligation was carried out bilaterally in each instance. Peritoneum was closed primarily following cystolysis and hypogastric ligation. Subsequent transsacral cystectomy was effected with much more facility in this group.

Group 3. Transsacral cystectomy was accomplished in 6 patients with earlier stages of bladder malignancy, involving only submucosal and superficial muscular layers of the bladder, not extending through the bladder wall or into the adjacent pelvic tissues. In all of these cases, ileal conduit urinary diversion was accompanied by cystolysis and extraperitonealisation of the bladder combined with bilateral hypogastric arterial ligation. Transsacral cystectomy was accomplished with ease in this group, operative time averaging 2 hours, and there were no immediate or delayed postoperative complications.

Conclusion

When a 2-stage procedure has been selected transsacral cystectomy is a rational alternative approach for the removal of the urinary bladder for palliation or cure of malignancy. This approach may be preferred because of multiple previous intra-abdominal operations, previous radiation therapy compromising the anterior abdominal wall, obesity of the patient, poor condition of the patient or other factors. The transsacral approach has limitations, however, particularly with regard to node dissection.

Summary

The transsacral approach for 2-stage cystectomy has advantages in certain cases.

The operative technique is described.

19 patients were treated by this method with satisfactory results when the bladder had been partly mobilised at the first stage.

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Symptomatology, Pathophysiology and Treatment of the Transurethral Resection of the Prostate Syndrome

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A well-known but fortunately infrequent complication occurring during transurethral resection of the prostate (TURP) is the sudden change in serum electrolyte concentrations resulting from the rapid absorption of large amounts of urologic irrigating fluid through open prostatic venous channels. The rapid decrease in serum cation and anion concentrations and the marked expansion of the extracellular fluid volume (ECF) result in a clinical syndrome, the TURP reaction, typically characterised by headache, nausea, vomiting, muscular twitching, cardiac arrhythmias, disorientation, convulsive seizures and occasionally death. While this syndrome has been widely recognised, the alterations in pathophysiology and the treatment of this syndrome are less well appreciated. Earlier studies indicated that ECF changes in patients undergoing TURP who did not develop the syndrome were quite variable, ranging from only a few millilitres to 2 to 3 litres (Taylor *et al.*, 1958; Beirne, Madsen and Burns, 1965; Emmett, Gilbaugh and McLean, 1969; Desmond, 1970; and Mebust, Brady and Valk, 1970). Prior studies were limited in that extracellular volume change could be calculated only from changes in serum sodium and chloride ion concentrations or weight gain. This report deals with the syndrome as it occurred in 5 patients undergoing transurethral resection of the prostate, and contrasts not only the changes in serum electrolytes but also the changes in the absorbed irrigating fluid in the serum—from the onset of the syndrome until clinical recovery or death—with 8 control patients undergoing the same procedure. In addition, the clinical signs and symptoms that occurred at the onset of the syndrome will be discussed and a successful therapeutic approach to the syndrome based on the altered pathophysiology will be outlined.

Patients and Methods

Between 1966 and 1972, 319 transurethral resections of the prostate were performed at the Seattle Veterans Administration Hospital by urology residents.

Control Patients. Eight patients undergoing elective TURP were randomly selected for the control series. Summary of the data collected is presented in Table I. Blood was collected preoperatively, during the period of resection if it extended over 1 hour, immediately at the end of the resection and at intervals until serum values had returned to preoperative levels. In addition, a patient with chronic azotaemia was specifically studied.

Patients with Dilutional Hyponatraemia and Hypervolaemia. During the last 6 years 5 patients undergoing TURP have absorbed an unusually large amount of irrigating solution. The first 2 patients died in the immediate postoperative period; the next 3 survived and were studied until their serum values returned to normal.

Table I

Comparison of 8 Control Patients and 5 Patients Who Absorbed Large Amounts of Irrigating Fluid During TURP (Mean $\pm$ S.E.).

	Controls	Patients Developing Syndrome
Age (years)	73.1 $\pm$ 3.4	74.4 $\pm$ 2.7
Weight (kg)	71.6 $\pm$ 3.8	61.6 $\pm$ 3.5*
Length of time of resection or until start of TURP syndrome (minutes)	69 $\pm$ 10	67 $\pm$ 17
Grams of prostate resected	18 $\pm$ 4	35 $\pm$ 13
Preoperative serum sodium (mEq/l)	139 $\pm$ 2	135 $\pm$ 6
Postoperative serum sodium (mEq/l)	138 $\pm$ 3	99 $\pm$ 7*
Preoperative serum chloride (mEq/l)	102 $\pm$ 3	97 $\pm$ 6
Postoperative serum chloride (mEq/l)	102 $\pm$ 3	76 $\pm$ 7*
Preoperative serum Cytal (mg/100 ml)	4 $\pm$ 0.7	2 $\pm$ 2.3
Postoperative serum Cytal (mg/100 ml)	31 $\pm$ 9	894 $\pm$ 157*
Change in ECF based on serum sodium (ml)	127 $\pm$ 245	4,540 $\pm$ 900*
Change in ECF based on serum chloride (ml)	186 $\pm$ 259	3,600 $\pm$ 800*
Change in ECF based on serum Cytal (ml)	153 $\pm$ 40	4,900 $\pm$ 1,200*
Preoperative serum osmolality (mOsm/kg)	295 $\pm$ 7.8	N.A.†
Postoperative serum osmolality (mOsm/kg)	297 $\pm$ 4.4	297 $\pm$ 15.1

* $P < 0.001$.

† Not available.

Chemical Determinations. The irrigating solution used in all resections was Cytal^R (Cutter Laboratories)¹ Cytal contains 2.7 g/100 ml of sorbitol and 0.54 g/100 ml of mannitol, a total 6-carbon alcohol concentration of 3.24 g/100 ml. This solution has a milliosmolality of 178 mOsm/kg and contains no electrolytes. Serum concentration of the two 6-carbon alcohols (referred to throughout this paper as serum Cytal levels) was determined by the method of Bailey (1959) as modified for processing in the auto-analyser.

This method measures only total concentration of the 6-carbon alcohols, therefore it is impossible to compare changes in mannitol or sorbitol individually. Serum sodium and potassium concentrations were determined by flame photometry, chloride by the Cotlove chloridometer and bicarbonate by the microgasometric procedure. Serum osmolality was measured by freezing point depression with a Fiske osmometer.

Calculation of extracellular fluid volume changes. The general formula $x = \frac{A(C-D)}{B-D}$ was used to calculate changes in ECF.

x = change in ECF in litres (a positive value denotes an increase, a negative number a decrease in ECF).

A = preoperation ECF in litres, equal to 20% of the patient's weight.

B = post-resection concentration of sodium, chloride or Cytal in serum.

C = preoperation concentration of sodium, chloride or Cytal in serum.

D = concentration of sodium (0 mEq/l), chloride (0 mEq/l) or Cytal (3,2400 mg/100 ml) in the irrigating fluid.

Results

Control Group

Four of the control patients demonstrated a slight decrease in serum sodium and chloride immediately following resection and 4 showed a similar increase. All 8 patients had a slight

¹ While Cytal was used exclusively in these studies, we would anticipate that the excessive absorption of any non-electrolyte osmotically active irrigating solution would cause similar pathophysiological responses.

elevation in serum Cytal at the end of resection (Table I). Calculations indicate that the increase in ECF was negligible (155 ml). No significant change was seen in serum potassium, bicarbonate or osmolality. Seven patients had subarachnoid block and 1 had a general anaesthetic. The average time of anaesthesia was 126 minutes. The average time for vasectomy was 20 minutes and for resection 69 minutes. All the specimens were histologically benign and averaged 18 g in weight. The estimated average blood loss was 100 ml. During the 2 hours of anaesthesia the patient received an average of 450 ml of intravenous fluid (either 5% dextrose and water or 5% dextrose and Ringer's lactate).

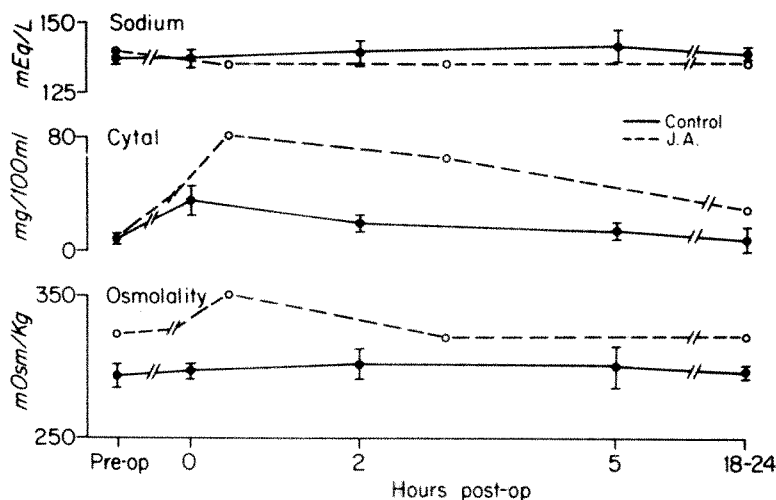


Fig. 1. Temporal changes in serum sodium, serum Cytal and serum osmolality after TURP of 8 control patients and 1 patient (J. A.) with chronic azotaemia. (Values are mean $\pm$ S.E.)

The temporal changes in serum sodium, serum Cytal and serum osmolality are summarised in Figure 1. No significant change was seen in the serum sodium or serum osmolality. The serum Cytal was highest immediately after completion of the resection (31 mg/100 ml). It had decreased to 15 mg/100 ml by 2 hours post-resection. By 5 hours after the resection it was 9.6 mg/100 ml, and by 18-24 hours it had returned to preoperative levels.

One 56-year-old patient, J. A., was specifically studied because of chronic azotaemia. His BUN stabilised at 50 mg/100 ml on catheter drainage. During the TURP he received 400 ml of 5% dextrose and Ringer's lactate. While serum sodium and chloride only decreased 2 mEq/l, serum Cytal increased from a preoperative level of 5 mg/100 ml to 76 mg/100 ml immediately after resection. In 24 hours it returned to nearly normal levels (Fig. 1). Calculations based on serum Cytal revealed an ECF expansion of 280 ml.

Patients who Developed the TURP Reaction

Five patients absorbed extremely large amounts of fluid. The average increase in ECF was 4.3 litres. The average decrease in serum sodium was 36 mEq/l, the average decrease in serum chloride was 21 mEq/l and the average rise in serum Cytal was 892 mg/100 ml. No change occurred in serum potassium. Serum bicarbonate decreased from a preoperative average of 28 mEq/l to 17 mEq/l at the onset of the reaction. Two hours later, it had returned to preoperative levels. No significant variations occurred in the patient's serum osmolality.

Case 1. C. W. R. was a 70-year-old patient with chronic azotaemia (BUN 63 mg/100 ml) and lower urinary tract obstruction. A TURP was performed. After 60 minutes of resection, the patient experienced severe chest pain and

hypotension. The anaesthetic was changed from continuous peridural anaesthesia to inhalation anaesthesia when he developed erratic behaviour which could not be controlled with sedation. Heavy prostatic fossa bleeding was noted and an additional 50 minutes of fulguration of the prostatic fossa ensued. EKG revealed no evidence of acute changes. Serum sodium at the end of the fulguration was 83 mEq/l, a decrease of 32 MEq/l from his pre-operative value of 115 mEq/l (Table II). The patient was given approximately 400 ml of hypertonic saline and 5 units of blood because of continued heavy bleeding. Eight hours later, the patient developed cardiac arrest and could not be resuscitated. Autopsy permission was denied. Calculations of changes in ECF based on serum sodium and chloride indicated an increase of ECF of 4.6 and 4.1 litres respectively.

Table II

Changes in Serum Sodium and Serum Cytal of Patients Developing the TURP Syndrome

	Weight (kg)	Serum Sodium (mEq/l)		Serum Chloride (mEq/l)		Serum Cytal (mg/100 ml)		Increased ECF (litres) Based on Serum		
		Pre- operative	Post- episode	Pre- operative	Post- episode	Pre- operative	Post- episode	Sodium	Chloride	Cytal
Case 1	60.0	115	83	75	56	N.A.*	N.A.*	4.6	4.1	N.A.*
Case 2	60.9	143	90	104	70	0	1,195	7.2	5.9	7.1
Case 3	53.6	136	104	99	83	8	880	3.3	2.1	4.0
Case 4	60.9	139	116	107	93	0	540	2.4	1.8	2.4
Case 5	72.7	141	104	100	78	0	960	5.2	4.1	6.1
Mean SE	61.6 ± 3.5	135 ± 6	99 ± 7	97 ± 6	76 ± 7	2 ± 2.3	894 ± 157	4.5 ± 0.9	3.6 ± 0.8	4.9 ± 1.2

* Not available.

Case 2. A. K. F. was an 80-year-old man who had a TURP and vasectomy for acute urinary retention. A perforation was noted in the prostatic capsule early in the operation. 70 minutes after the start of the operation the patient became restless and complained of abdominal pain. Resection and fulguration were continued for another 25 minutes. The patient became unresponsive although his vital signs were stable. He had received 600 ml of 5% dextrose in normal saline and 700 ml of whole blood. Serum sodium drawn at this time was 90 mEq/l (Table II). Whole blood and 3% sodium chloride was given. The blood pressure began to fall and in spite of vigorous supportive therapy the patient expired of cardiac arrest.

Autopsy revealed 800 ml of ascitic fluid and bilateral pleural effusions of 200 ml. The ascitic fluid Cytal concentration was 2,227 mg/100 ml, the pleural effusions 1,065 mg/100 ml. Marked pulmonary congestion and oedema increased the lung weight to 3 times normal (800 g and 820 g). Calculations based on serum sodium revealed an increment in ECF of 7.2 litres, based on serum chloride of 5.9 litres, and based on serum Cytal of 7.1 litres.

Case 3. J. L. was a 75-year-old male with carcinoma of the prostate who was admitted in urinary retention. A TURP was performed in 40 minutes. Immediately prior to the completion of the resection heavy venous bleeding was noted. The patient developed convulsions, the operation was stopped and a catheter placed in the bladder. Serum sodium was immediately drawn and was 104 mEq/l (Table II). All intravenous fluid therapy was discontinued. He did not develop hypotension. By 1½ hours' post-resection the serum sodium had risen to 113 mEq/l and the serum Cytal had decreased from 880 mg/100 ml to 452 mg/100 ml. By 2½ hours' post-resection, the serum sodium had increased to 131 mEq/l, the serum Cytal had decreased to 162 mg/100 ml. By 18 hours' post-resection all values had returned to preoperative levels. Changes in serum chloride paralleled those of serum sodium. Calculations revealed an increment in ECF of 3.3 litres based on serum sodium, 2.1 litres based on serum chloride and 4.0 litres based on serum Cytal concentrations.

Case 4. J. F., a 79-year-old white male, had a TURP under subarachnoid block for acute urinary retention. Serum sodium was normal at 15 and 30 minutes from the beginning of the resection. At 40 minutes he complained of upper abdominal pain and a capsular perforation was observed. Atrial and ventricular arrhythmias were noted. The resection was carried on for an additional 5 minutes until a third serum sodium was reported at 116 mEq/l (Table II). All fluid therapy was stopped. The arrhythmias disappeared following treatment with lidocaine hydrochloride and procainamide hydrochloride. Blood loss was estimated at 70 ml. The patient received no blood and only 500 ml of

5% dextrose and Ringer's lactate. By 2 hours after surgery serum sodium had increased to 128 mEq/l and the serum Cytal had decreased from 540 mg/100 ml to 139 mg/100 ml. By 29 hours after surgery all values had returned to preoperative levels.

Case 5. F. D. was a 68-year-old white male who had a TURP for acute urinary retention. 90 minutes after starting the resection he complained of some suprapubic pain and became hypotensive and restless; serum sodium at this time was 136 mEq/l. 30 minutes later 4 areas of perforation were noted in the prostatic capsule. At this moment the patient developed convulsions. Serum sodium was 104 mEq/l (Table II). All fluid therapy was discontinued. By 1½ hours' post-resection the serum Cytal had decreased to 113 mEq/l. These gradually returned to preoperative levels by 22 hours after surgery.

Calculations revealed an increment in ECF based on serum sodium of 5.2 litres, based on serum chloride of 4.1 litres and based on serum Cytal of 6.1 litres. The amount of blood and fluid infused during surgery was 1,400 ml.

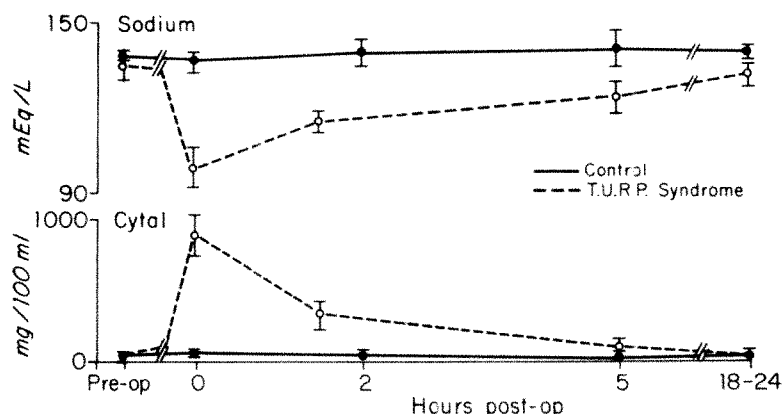


Fig. 2. Comparison of the temporal changes in serum sodium and serum Cytal of patients who developed the TURP syndrome with the control patients. (Values are mean $\pm$ S.E.)

Discussion

The sudden absorption of a large volume of sodium free, osmotically active urologic irrigating solution resulted in rapid expansion of the intravascular volume and marked hyponatraemia. Ultimately, this fluid was distributed throughout the total ECF. As with mannitol alone (Kleeman and Fichman, 1967), a rapid osmotic diuresis ensued if the cardiovascular system was not overwhelmed by the huge volume load. In our surviving patients, serum Cytal values had fallen 90% and serum sodium risen (20%) in 5 hours (Fig. 2). Thus the situation was self-correcting if recognised immediately and treated appropriately.

We were unable to find any factor that indicated prior to the resection, who would develop the syndrome. The only significant difference between the 2 groups was that the patient who developed the syndrome weighed an average of 10 kg less than the controls (Table I). While the amount of tissue resected from the patients who developed the syndrome was greater than the controls, the difference was not statistically significant.

Obviously it is essential that the syndrome be recognised early and adequate therapeutic measures followed. One of the earliest symptoms that our patients developed was restlessness and pain (Table III). The pain occurred in the field of the spinal anaesthetic or was located in the anterior chest. Abdominal pain probably resulted from perforation of the prostatic capsule and extravasation of fluid. Perforation of the prostatic capsule does not invariably initiate the TURP syndrome, however. As demonstrated by Case 5, a capsular perforation was noted 90 minutes into the resection when the patient complained of lower abdominal pain. Only minor changes were found in the patient's serum values at that time.

Two of our patients had no complaints; the presence of the syndrome was indicated by seizures.

Heavy prostatic fossa bleeding, however, was noted in 1 of these patients. Because of this experience it is now our policy to obtain serum sodium values and terminate the procedure whenever unusual signs or symptoms occur in patients undergoing TURP. Following these simple precautions none of the patients undergoing TURP in this hospital has developed the syndrome during the last 2½ years.

The irrigating fluid was initially distributed in the intravascular space. As documented in Case 2, where high concentrations of Cytal were found in the pleural and ascitic fluids, it was then distributed throughout the entire ECF space. While the syndrome developed in 1 patient who absorbed only 2.4 litres of irrigating fluid, all the other patients increased their ECF volume much more. The unusually severe hyponatraemia, which developed so suddenly may have precipitated electrical disturbances at the membrane level. Cardiac arrhythmias and seizures

Table III
Clinical Presentation of Patients with TURP Syndrome

	Resecting Time Minutes	Symptoms and Signs
Case 1	60	Chest pain, shortness of breath, hypotension
Case 2	70	Restlessness, moderately severe lower abdominal pain
Case 3	40	Heavy venous bleeding, seizures
Case 4	40	Upper abdominal pain, cardiac arrhythmias
Case 5	125	Seizure

often resulted, though the seizures might have been secondary to decreased cerebral perfusion during an arrhythmia and not to the membrane effect.

The pattern of serum sodium, chloride and Cytal changes that occurred in the patients developing the syndrome was quite different from the controls (Fig. 2). A reciprocal relationship between serum Cytal and serum sodium was evident. In the 3 patients who survived the episode, there was a rapid decrease in serum Cytal. Five hours after the onset of the syndrome, only 10% of the Cytal remained in the blood. The return of the serum sodium or chloride values was much slower, requiring 18 to 24 hours to return to preoperative levels, indicating that final restoration of the patient's ECF required 24 hours. The rapidity of development of this problem indicates that the "inappropriate" response of antidiuretic hormone was not significantly involved.

While 6-C alcohols are metabolised by the liver (Ellis and Krantz, 1941; Bye, 1969), patient J. A. demonstrated the importance of renal clearance of Cytal. His poor renal function resulted in a significantly higher serum level and longer retention of Cytal than other control patients (Fig. 1). Should such a patient develop the full syndrome, dialysis would probably be required.

No statistically significant difference in ECF increment could be found using the changes in 3 different substances in the blood. Calculations based on serum Cytal values probably are the most reliable measurement of changes in ECF, as 6-C alcohols are usually not present in serum. The changes in serum sodium and chloride during resection were affected by intravenous therapy. In addition, chloride ion shifts that occurred between the erythrocytes and serum during preparation of blood for serum sodium and chloride determination also affected the results.

As illustrated by Cases 1 and 2, death from the syndrome does not occur immediately. What is important is that while the syndrome occurs quickly there is still time to prevent a fatal outcome. The successful treatment of these patients included immediate termination of the resection if the syndrome was clinically manifested or the serum sodium was significantly decreased. Prostatic fossa bleeding was controlled by inflated Foley catheter and traction if necessary. Cessation of all fluid therapy was mandatory. While experimental (Drinker *et al.*, 1963) and

clinical (Kunin and Limbert, 1969) evidence has suggested that the use of hypertonic saline may be advisable, our experience indicates that it is best not to use this substance. The experimental evidence, unfortunately, was based on healthy animals with large cardiac reserves. Administration of hypertonic saline will only add more volume to an already heavily compromised circulatory system. The first 2 cases were treated with 3% saline in amounts up to 400 ml (which is equivalent to an additional 1.4 litres of extracellular fluid). Both died, and in 1, death clearly was due to volume overload. Correction of the hyponatraemia, then, should be left to the osmotic diuresis which occurred promptly. When seizures or arrhythmias persisted, pharmacologic agents were used to correct them. Using this approach a prompt correction of the physiologic disturbance occurred in the last 3 patients.

Summary

Five patients who developed the TURP syndrome during transurethral resection of the prostate absorbed an average of 4.3 litres of urologic irrigating fluid (Cytal). The serum sodium and chloride decreased an average of 36 and 21 mEq/l respectively. The serum Cytal increased an average of 892 mg/100 ml.

In comparison minimal changes occurred in the serum values of 8 control patients undergoing TURP.

Pain in the previously anaesthetised area, seizures, cardiac arrhythmias or heavy prostatic venous bleeding occurred just before the onset of the reaction.

Successful treatment included the immediate termination of the resection, control of haemorrhage with Foley catheter and traction, and cessation of all intravenous therapy. The administration of hypertonic saline is contraindicated. Using this method of treatment the serum Cytal levels returned to preoperative values in 5 hours; serum sodium and chloride returned to preoperative levels 24 hours after the resection.

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The Effect of Prostatectomy on the Symptoms and Signs of Benign Prostatic Hypertrophy

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After placebo medication patients with benign prostatic hypertrophy improve significantly (Damrau, 1962; Castro, 1972a). In this study the effects of open prostatectomy on subjective and objective measurements have been examined and compared with the effects of placebo medical treatment given to the same patients.

Methods

Seven patients who received placebo medication as part of a double blind, controlled clinical trial of spiorolactone for the treatment of benign prostatic hypertrophy (Castro, Griffiths and Edwards, 1971) subsequently required open prostatectomy. Five of them had a retropubic prostatectomy and 2 had a transvesical operation. The diagnosis of benign hyperplasia was confirmed histologically in all cases.

Each patient underwent 4 assessments; 1 before the placebo was started and another after 6 months of placebo treatment; the third was at least 1 month after placebo had been stopped and within 1 week of prostatectomy, and the final assessment was at least 1 month after surgery. At the time of these examinations the urine was sterile and patients were not taking drugs known to affect the urinary tract (Feaver, Usher and MacEwan, 1967).

At each assessment a total symptom score was obtained by adding together the grades (0-3) of urgency, hesitancy, dysuria and dribbling, and of the urinary stream (3-0) as assessed by the patient (Castro, Griffiths and Shackman, 1969). Frequency (the total number of voidings in 24 hours) and nocturia (the number of voidings during the patient's normal resting period) were recorded for 1 week and mean daily values deduced.

Simultaneous measurements of intravesical pressure and urinary flow rate were made (Von Garrelts, 1956; Castro and Griffiths, 1972b). From the intravesical pressure recordings measurements were made of the resting pressure (defined as the lowest value before or after micturition) and also the average and maximal pressures during micturition. These measurements were made twice at each assessment and mean values calculated. The volume of urine voided at each act was also recorded during the measurements of urinary dynamics (Griffiths and Castro, 1970).

The change in response to operation was compared to the effect of placebo.

Results

The effects of prostatectomy on subjective and objective measurements for individual patients are shown in Table I. Mean values for the group of patients are shown in Table II. When the effects of operation were compared with the effect of a placebo given to the same patient for 6 months the results of surgery were very much better.

After prostatectomy the mean symptom score decreased from 6.6 to 1.4, a difference of –5.2 which was significantly ($P = 0.05$) better than the change of –1.2 due to placebo. Frequency

Table I
Measurements before and after Open Prostatectomy

Type of Op.		Total Symptom Score	Frequency (Voidings/24 hr)	Nocturia	Bladder Pressures (mm Hg)				Flow (ml/sec)	Volume (ml)
					Resting	Commencing	Av.	Max.		
R.P.P.	Pre-op.	8	10.1	3.3	28.0	76.0	60.0	84.0	14.9	330
	Post-op.	2	8.5	2.0	36.0	29.3	25.9	29.3	21.1	320
T.V.	Pre-op.	5	15.4	6.3	17.5	30.5	32.5	32.5	7.5	550
	Post-op.	4	9.0	4.5	24.9	33.3	48.3	48.3	8.5	350
T.V.	Pre-op.	5	13.2	6.7	26.7	90.0	80.0	100	8.2	1
	Post-op.	0	7.0	1.5	8.8	19.0	19.0	19.0	32.0	380
R.P.P.	Pre-op.	7	8.1	0	45.7	106	106	120	5.1	110
	Post-op.	0	4.0	0.5	30.3	44.3	43.0	51.0	23.6	400
R.P.P.	Pre-op.	10	6.6	1.9	28.9	111.1	111.1	111.1	1.8	200
	Post-op.	1	6.0	0	31.8	43.0	41.9	43.0	6.6	320
R.P.P.	Pre-op.	5	15.0	3.1	32.5	102.5	75.0	100	4.5	180
	Post-op.	1	4.5	1.0	38.0	38.0	38.0	38.0	50.0	400
R.P.P.	Pre-op.	8	13.4	7.4	32.0	80.0	93.3	94.3	6.0	150
	Post-op.	2	4.5	1.0	43.9	45.3	45.9	47.3	22.5	190

T.V. = Transvesical prostatectomy.

R.P.P. = Retropubic prostatectomy.

Table II
The Effects of Prostatectomy on Prostatic Symptoms and Signs (mean values)

Mean Values	Symptom Score	Frequency	Nocturia	Bladder Pressures (mm Hg)				Flow (ml/sec)	Volume (ml)
				Resting	Commencing	Av.	Max.		
Before prostatectomy	6.6	13.1	4.9	30.2	85.2	79.7	91.7	6.9	261.4
After prostatectomy	1.4	6.2	1.5	30.5	36.0	37.4	39.3	23.5	337.1
Change due to operation	-5.2	-6.9	-3.4	+0.3	-49.2	-42.3	-52.4	+16.6	+75.7
Placebo change	-1.2	-1.3	-0.5	+11.3	+13.5	+44.4	+14.6	+0.6	-3.5
P values	0.05	0.001	0.05	0.01	0.05	0.05	0.01	...	...

P values comparing the effects of operation and placebo are given.

was also less after surgery; the mean value for 24 hours decreasing from 13.1 to 6.2; an improvement which was considerably ($P = 0.001$) better than seen after placebo (-1.3). Nocturia decreased from 4.9 to 1.5 after operation and this result was again significantly better ($P = 0.05$) than that following placebo (difference -0.5).

Resting bladder pressures before and after prostatectomy were almost the same, but the intra-vesical pressures during micturition were lower after surgery. In contrast, all bladder pressures had increased during 6 months of placebo. The rate of urinary flow and the total volume voided

were much improved after surgery and these changes were considerably better than the small effects of placebo.

Discussion

There was significant improvement of all the subjective and objective measurements after prostatectomy. When these effects were compared to the changes after placebo, surgery was significantly better in every aspect.

After operation the total symptom score and frequency of micturition improved in all 7 patients and nocturia improved in the 6 patients showing this symptom pre-operatively. It would seem that prostatectomy is useful in the management of frequent micturition associated with benign prostatic hypertrophy, at least in patients who also have symptoms of obstruction.

Mean resting bladder pressure did not change significantly after surgery; in 5 patients there was a slight increase, in 2 a slight decrease. These data agree with those of Smith (1968) who found no change in 2 and a fall of pressure in 1 patient. In 6 of 7 patients commencing, average and maximal pressures were all less after surgery and this is similar to the findings of Smith (1968) and also the 5 patients described by Holm (1964). Six of our patients had maximum bladder pressures above the normal range (Von Garrelts, 1957) before operation, but after surgery they fell to be within it.

The maximal urinary flow rate of all patients was below the normal range (Sandoe, Bryndorf and Gertz, 1959; Castro, unpublished) before surgery and the increase seen in every patient after it is similar to the findings of others (Brantley-Scott *et al.*, 1967). In 5 of 7 patients the increase was enough to bring flow to the normal range, but 2 patients remained within the range described for prostatic patients (Castro and Griffiths, 1972c). Both patients with low pre-operative flow rates described by Smith (1968) and 3 of the 5 described by Holm (1964) reached normality after prostatectomy.

The maximal urinary flow rate of 1 patient after surgery was above the upper range of normal and it has been suggested that this results from hypertrophied detrusor muscle or improved funnelling of the proximal urethra in the post-prostatectomy patient with an open prostatic urethra (Brantley-Scott, *et al.*, 1967).

It has been shown previously that 6 months' treatment with placebo improved symptom score in 76% of patients, frequency in 71% and nocturia in 62%. Maximal intravesical pressure increased significantly ($P = 0.02$) and urinary flow rate was unchanged (Castro *et al.*, 1971). However, the present study shows that despite these impressive changes due to placebo the effects of surgical prostatectomy are significantly better.

Summary

Subjective and objective measurements were made in 7 patients before and after open prostatectomy and the results were compared to the effects of placebo given to the same patients.

The effect of prostatectomy was to decrease symptoms, frequency and nocturia. Resting bladder pressure was unchanged, but pressures measured during micturition were lower. The maximal urinary flow rate and volume voided were much improved after operation.

When the effects of operation were compared with the effects of placebo, the results of surgery were very much better.

These data were included in a thesis presented to London University for the degree of M.S. I wish to thank Mr D. Edwards who helped with the statistical analysis, G. D. Searle & Co. Ltd, who gave financial support, and Mr G. D. Chisholm, under whose care the patients were admitted.

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Tuberculosis of the Male Urethra

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Tuberculosis of the male urethra is very uncommon: a review of the literature of the last 20 years reveals only 16 case reports (Dourmashkin, 1952; Ross, 1953; Le Brun, 1958; Campbell and Harrison, 1970; Chambers, 1971). If strictures occur in the diagnosis or treatment of genitourinary tuberculosis, it is not always clear whether they are due to instrumentation or to the specific infection: *e.g.* O'Flynn (1970) had 10 instances of urethral stricture in 762 cases with genitourinary tuberculosis, but they all responded in the usual way to intermittent dilatation while having chemotherapy. In Ross's series of 469 men with genitourinary tuberculosis, only 9 had urethral involvement, though more than half the cases had genital disease. When considered among other likely causes of the unusually difficult or intractable urethral strictures which call for urethroplasty (Blandy *et al.*, 1971, 1972), again tuberculosis does not appear to be a common cause, and the 4 such cases reported here were drawn from a larger series of 112 patients coming to urethroplasty over a period of 8 years. Since these cases are so rare, and since they present certain problems in diagnosis and management, we have thought it justifiable to report our experience of 5 cases in which the urethra appeared to have been involved in mycobacterial infection.

Case Reports

Case 1. S. H. aged 64 (No. 54398). In 1966 this patient developed an abscess in the right side of the scrotum which was incised and then healed spontaneously. A year later he began to have increasing frequency of micturition and infrequent watery stools, and developed a large perineal abscess which seemed to be continuous with the prostate, which was enlarged and fluctuant. When this was aspirated, *M. tuberculosis* was isolated both from the pus and from the urine. The pyelogram showed no renal disease. The chest radiograph showed shadowing and calcification at both apices, but the sputum failed to grow *M. tuberculosis*. A urethrogram showed some narrowing of the posterior urethra with spontaneous filling of the rectum through an irregular fistula (Fig. 1). A suprapubic cystostomy was performed and he was treated with a complete course of streptomycin, PAS and INAH. Over the next 18 months all the local signs of inflammation subsided. He continued however to pass urine per rectum, and in addition had recurrent secondary infections with *B. proteus*. Eventually the time seemed to have come to close the fistula, but at preliminary sigmoidoscopy, the rectal opening of the fistula was discovered to contain a small calculus. The stone was easily dislodged with the finger. After this the fistula healed promptly. Later a transurethral resection of the remnant of his obstructing prostatic tissue was performed—removing tissue which showed only benign hyperplasia, but no evidence of tuberculosis. 12 days later his suprapubic catheter was removed and he regained normal micturition. His fistulas remained closed ever since.

Case 2. R. E. aged 16 (No. 285304) (Fig. 2). At the age of 10, in 1960, this boy presented with bilateral tuberculous epididymitis and a long anterior urethral stricture. Pyelography showed a non-functioning left kidney with a calcified ureter. *M. tuberculosis* was isolated from the urine. After an 18-month course of triple therapy with streptomycin, PAS and INAH, his left kidney was removed. His urethral stricture was then treated over the next 5 years with regular dilatations together with local instillations of hydrocortisone. Because of the need for frequent and difficult dilatations, a complete urethroplasty was performed in 2 stages.

After the closure of the anterior part of the urethroplasty a fistula persisted and required formal closure 6 months later. Histological examination of the excised tissue did not show any residual evidence of tuberculosis.

Case 3. M. S. aged 21 (No. 5855/57) (Fig. 3). At the age of 13 this man developed tuberculosis and underwent a right nephrectomy. Three months later he was found to have an anterior urethral stricture, and from then on underwent periodic dilatation, always with considerable difficulty. The dilatations were performed at 6 weekly intervals under general anaesthesia. In 1964 a first stage urethroplasty was performed, but revised a year later

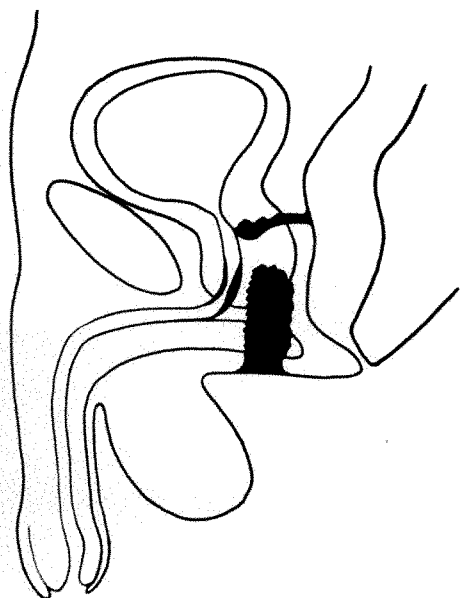


Fig. 1. Case 1. Diagram of the urethral and prostatic lesion: a prostatic abscess communicated with the cold abscess in the perineum, and formed a fistula into the rectum.

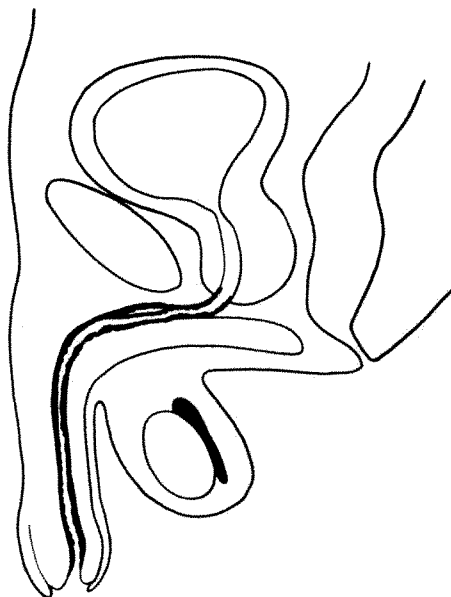


Fig. 2. Case 2. Diagram to show extent of this long urethral stricture.

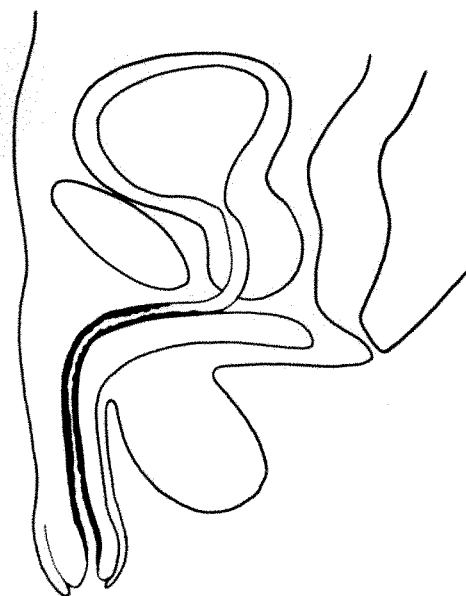


Fig. 3. Case 3. Diagram to show extent of urethral stricture.

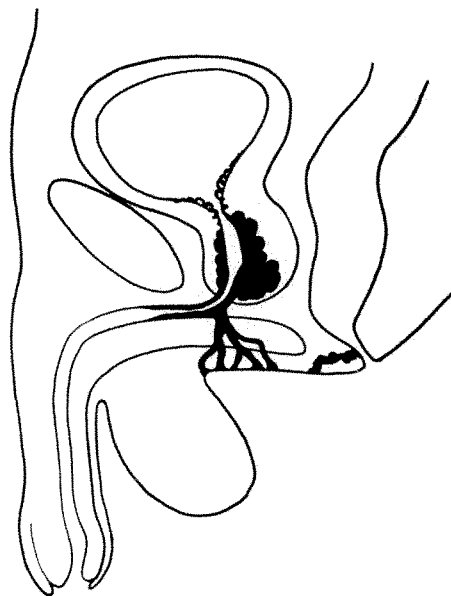


Fig. 4. Case 4. Condition on admission: a cavitated prostate with oedema on the floor of the bladder was associated with a watering-can perineum and a low-level fistula-in-ano.

because of some recurrence of stenosis at the apex of the flap. Eventually the second stage was performed (in January 1967) and even then a small fistula persisted in the anterior part of the suture line, for which 3 attempts at closure were carried out before success was achieved. He now has no symptoms and satisfactory sexual function.

Case 4. M. D. aged 24 (No. 524887) (Fig. 4). Three years before admission this patient was kicked in the perineum at football, and developed a swelling, which was explored. One year later he was found to have developed a urethral stricture, and this was treated by intermittent bouginage, and at least 1 external urethrotomy in another country. When he was admitted in 1969 he had hourly frequency, as well as incontinence, and was found to have a watering-can perineum with at least 5 fistulous openings. He had a constant purulent discharge from the urethra and in addition had a subcutaneous fistula-in-ano. Digital pressure over the boggy prostate yielded pus at the external meatus. The pyelogram showed ragged cavities in the right middle and lower calyces, and a thick-walled hypertrophied bladder. In spite of the clinical suspicion of tuberculosis, we were unable to isolate the *Mycobacteria* from any specimens of his urine, and for this reason, we withheld antituberculous therapy.

The first stage of his urethroplasty was performed in December 1969. The multiple sinuses and fistulae were excised. A scrotal flap was formed and the very unsatisfactory perineal skin was laid into the strictured urethra.

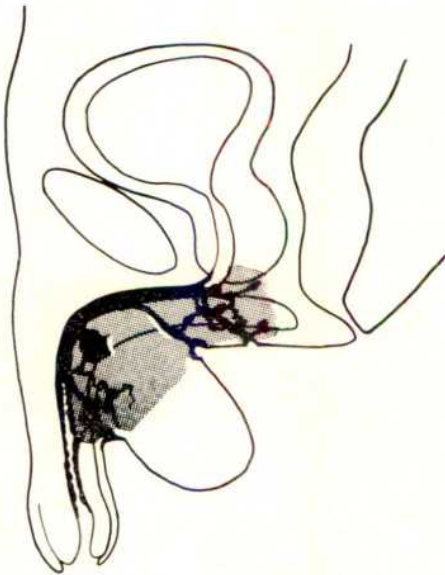


Fig. 5. Case 5. Diagram of the extent of the fistulae and the stricture.

His postoperative course was stormy: the flap became infected, oedematous and part of it underwent necrosis. The secondary infection was treated with ampicillin, but antituberculous therapy was still withheld. Eventually the wound healed. Histological examination of the excised sinuses was thought to rule out tuberculosis, and only to show a foreign body reaction. Despite the infection and partial necrosis of the scrotal flap, the urethroplasty healed. The patient's pain and strangury unfortunately continued without improvement and were attributed to secondary cystitis, since the bladder on cystoscopy was found to be grossly oedematous and inflamed. Repeated cultures of the urine still failed to grow *M. tuberculosis*.

After 2 months a second stage urethroplasty was performed, protected by a suprapubic cystostomy. Again healing was delayed and the wound remained indolent, the perineal fistula persisted for a month after closure of the urethroplasty. The fistula was then excised, and only now, for the first time, did histological examination show unequivocal evidence of tuberculous inflammation. Almost at the same time a positive report was received on 1 of the previous urine cultures. The patient was at once started on triple therapy with streptomycin, PAS and INAH.

His improvement was now very rapid: the symptoms abated as his inflamed bladder returned gradually to a normal appearance. His perineal suture line healed, leaving only 1 small sinus to be excised. As his general condition improved, he developed some pain and temporary obstruction to the right ureter, but this improved spontaneously. Two years later the patient remains well, with no urinary symptoms and satisfactory erections, but he has no ejaculate.

Case 5. W. K. aged 73 (No. 58886). Six years before admission to St Peter's this patient developed an abscess in his left groin, which gradually enlarged and "burst". Over the succeeding 6 years 1 abscess was followed by another,

until the penis, groins, scrotum and testicle had become cemented into a rigid mass, riddled with sinuses and fistulae. The penis was tethered by a tight chordee to the perineum. Radiographs of his chest showed extensive dense fibrosis of the left upper lobe with deviation of the mediastinum to the left side. His sputum grew *Mycobacterium kansasii* which was sensitive to cycloserine and ethionamide. We were never able to isolate this organism from the purulent discharge from his scrotum or from his urine, but this was presumably heavily overgrown with numerous other organisms, including *Pseudomonas pyocyanea*. The pyelogram showed normally functioning kidneys without any evidence of erosion of the calyces. The urethrogram showed multiple fistulae (Fig. 5).

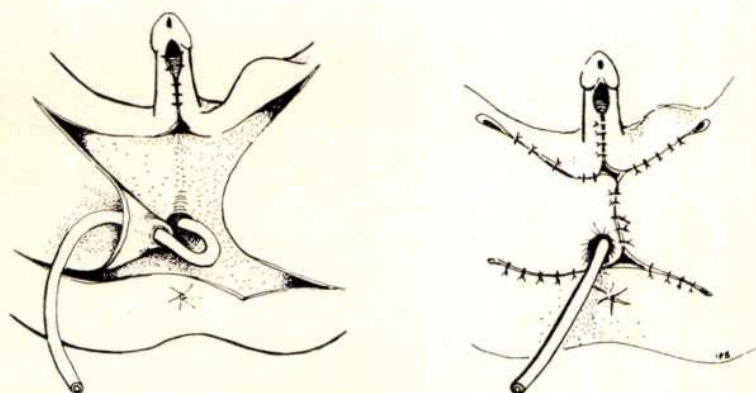


Fig. 6. Case 5. Steps in the later stages of reconstruction of the urethra after excision of the fistulae and the destroyed middle part of the urethra and corpus spongiosum. The right testis had previously been removed, and to release maximum scrotal skin the left one was placed in the groin. A scrotal flap was attached to a silastic tube and drawn up into the bladder.

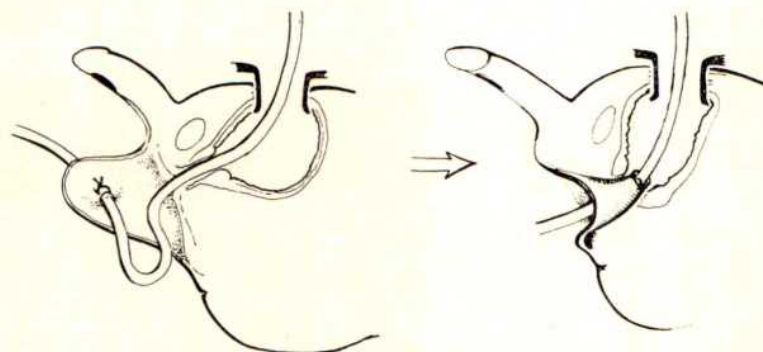


Fig. 7. Case 5. To show method of using the laterally-based scrotal flap as a "tent"—drawing it up into the bladder attached to the silastic tube.

A suprapubic cystostomy was performed first, and after 6 months, the fistulae and sinuses were excised, the chordee relieved by excising the contracted urethra, and the urethra reconstructed by means of a tent-shaped flap derived from the healthier right side of the scrotum. To do this it was necessary to put the left (remaining) testicle into the groin (Figs. 6-7). The urethra had been converted into a dense hard white cord, honeycombed with fistulae and sinuses, and only its last inch seemed to retain any semblance of a lumen. The histological examination of this tissue showed only chronic inflammatory changes, but no evidence of tuberculosis.

He recovered well after this and regained excellent micturition, through the perineal stoma. He was readmitted a year later to have the urethroplasty completed, but now was discovered to have an inoperable squamous cell carcinoma of the lung, and for this reason, the second stage was postponed, and he died with multiple metastases 4 months later.

Comments

Tuberculosis of the urethra is the result of spread from another focus, generally from higher up in the urinary tract, and usually, it seems, from the prostate. The urethra must be very resistant to tuberculosis, since it is so seldom involved, even though it conveys infected urine away from the bladder. Even when the prostate is involved, as it seems to be in as many as 70% of cases of genital tuberculosis (Warres, 1948), the urethra generally escapes infection.

Confirmation of the diagnosis is difficult: urine, prostatic fluid and semen may be contaminated by organisms from higher up in the genitourinary system, and even when there is a stricture, it may be difficult to attribute it to tuberculosis with any degree of certainty. In 3 of our patients we had isolated *M. tuberculosis* from the urine at some time in the past, but at the time their strictures were treated, the organism could not be found. In 1 patient (Case 4) the diagnosis was arrived at only after urethroplasty had been done, repeated and painstaking examination of urine and excised perineal tissue failing to provide evidence of tuberculous infection. In Case 1 the organism had been isolated not only from the urine but also from the perineal abscess with which the patient presented. In the last case (No. 5) we surmise, but cannot prove, that the infecting agent was originally *M. kansasii*. We consider that such a very complicated watering-can perineum in the absence of another cause, when combined with this unusual infection in the lungs, makes this a probable diagnosis.

The moral of this experience is that tuberculosis involving the urethra may present in bizarre and unexpected forms, either with fistulae of unusual types, or with strictures which respond unusually badly to conventional forms of treatment by urethroplasty. The diagnosis is not easy to prove, and it may be more common than a study of the literature leads one to suppose. Only by the combination of antituberculous therapy and surgery can tuberculosis of the urethra be remedied.

Summary

Five cases are described in which the urethra was involved in mycobacterial inflammation. The diagnosis is difficult to establish, and unless antituberculous therapy is given, surgical intervention is hazardous.

This paper was read at the meeting of the Section of Urology of the Royal Society of Medicine at The London Hospital on 25th May 1972. The authors are grateful to Messrs A. York Mason and F. R. Kilpatrick for their help with Case 1.

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Orchiolysis: Correction of the Undescended Testicle without Fixation

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"Orchidopexy" is derived from the Greek *pexis*, meaning to nail or peg, and in all textbooks describing the operation the need to fix or hold the testicle in the scrotum by one method or another is stressed (Rob and Smith, 1970; Bailey and Love, 1971; Scorer and Farrington, 1971; Farquharson, 1972).

Any method which applies tension to the testicle and cord or around the cord is contrary to a surgical principle and because of this Van Essen (1971) suggested that "orchiochalasy" (*chhalasis* (Gk)—to place or lower down) would be a more suitable name for an operation in which tension is not applied to the cord.

"Orchiolysis" (a freeing of the testicle by the division of any retaining bands) is a rather more euphonious alternative.

Manoeuvres such as division of the transversalis fascia medial to the internal ring, and ligation and division of the inferior epigastric vessels, have been practised under the impression that they allow the cord to straighten out and therefore increase its effective length. It is in fact the band of inelastic extraperitoneal fibrous tissue which forms the medial crus of the internal ring which should be divided if it is preventing the vessels from straightening out in their downward course. If this fibrous layer is divided, the underlying inferior epigastric vessels will easily be displaced medially and no advantage can be gained by dividing them. The vas is never the limiting factor in lengthening the cord and therefore attention should always be directed to proper mobilisation of the testicular vessels retroperitoneally above and behind the internal inguinal ring.

The operation of orchiolysis to be described is a simple one-stage operation paying careful attention to thorough mobilisation of the cord structures, so that the testicle may be placed into the scrotum without the need to employ any method for holding or fixing the testicle down.

Patients and Methods

During a 2-year period 42 patients were operated upon by the author for undescended testicle. In 8 patients the condition was bilateral, making a total of 50 testicles operated upon. In 20 cases the right testicle was affected, in 14 the left testicle, the remaining 8 patients having bilateral undescended testicles. The age of the patients ranged from 5 to 23 years, the average age being 11 years. Three patients had undergone a previous groin operation. One patient underwent emergency operation for torsion and successful orchiolysis was carried out.

At operation 28 testicles (56%) were of the obstructed variety, that is lying in the superficial inguinal pouch. 22 testicles (44%) were of the arrested or incompletely descended variety, 7 being found at the external ring, 12 in the inguinal canal and 3 at the internal ring. Orchiolysis was carried out on all 50 testicles, a hernial sac being removed in 15 cases (30%). The author has personally followed up all cases and results assessed taking into account position, size, consistency, mobility and sensation of the testicle.

Operative Technique

The testicle is exposed through a skin crease incision which extends far enough laterally to allow adequate exposure of the internal inguinal ring. With the testis held out of the wound under slight tension the cord structures come into view and a hernial sac if present is dissected off the front of the vessels and vas and ligated at the internal ring. The stump of the hernial sac or the edge of the peritoneum is lifted forwards and the plane between the peritoneum and the vas and vessels is developed. The testicular vessels and vas adhere to the peritoneum, being bound

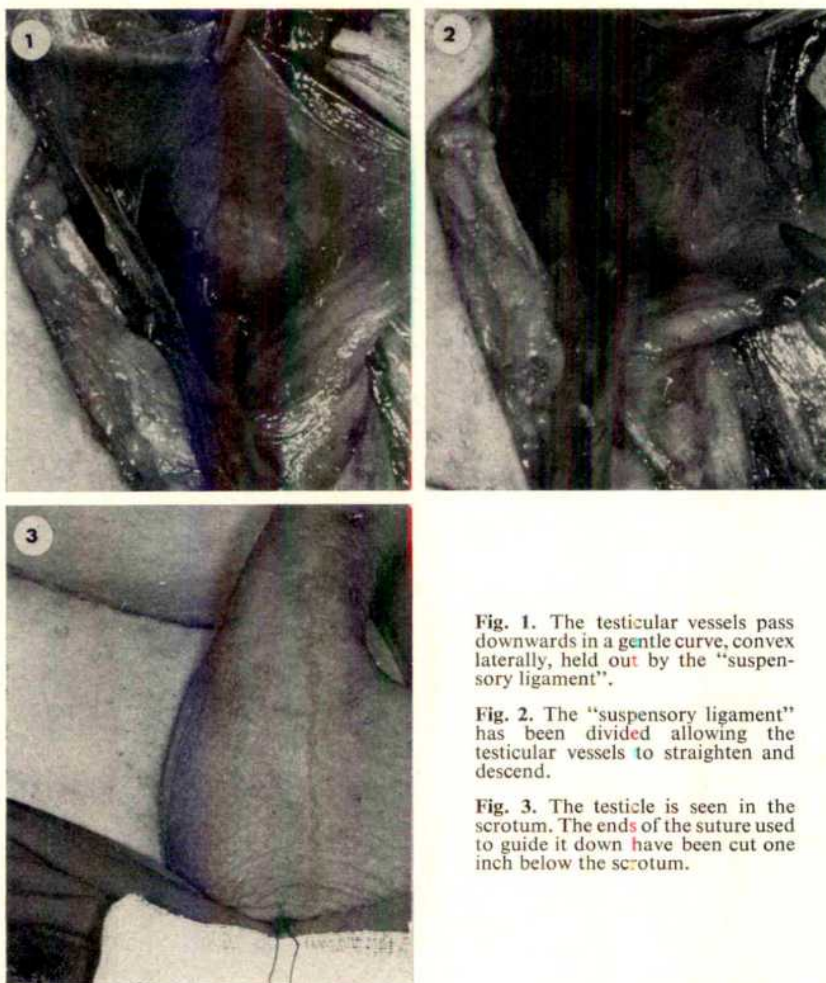


Fig. 1. The testicular vessels pass downwards in a gentle curve, convex laterally, held out by the "suspensory ligament".

Fig. 2. The "suspensory ligament" has been divided allowing the testicular vessels to straighten and descend.

Fig. 3. The testicle is seen in the scrotum. The ends of the suture used to guide it down have been cut one inch below the scrotum.

down to it by a sheet of extraperitoneal fibrous tissue. A fan-shaped condensation of suspensory fibres, the lateral suspensory ligament (Fig. 1), which spreads out from the testicular vessels holding them out laterally in a gentle convex curve is divided under direct vision with scissors. The plane is developed by blunt dissection both laterally and posteriorly to a higher level (Fig. 2). A further condensation of extraperitoneal fibrous tissue forms the medial crus of the internal inguinal ring and this is also carefully divided. This allows the vessels and vas to move medially and so further straighten out in their course through the inguinal canal. When the medial crus of the internal ring has been divided the inferior epigastric vessels become slack and move downwards and inwards with ease. No advantage would be afforded by dividing these vessels. This

dissection often produces an extra 3-4 cm of cord length by converting the course of the testicular vessels into a straight line, and in almost all cases this straightening leaves a definite amount of slack in the vas which is never the limiting factor in allowing the testicle to descend. Finally, with the cord still under slight tension all cremasteric muscle fibres and any fibrous bands are divided until only the vascular bundle and vas deferens remain. An absorbable suture is now used to transfix the anterior part of the gubernacular remnant, and after ligature both ends are left long; they will be used to guide the testicle down into the scrotum.

The pathway from the groin to the scrotum is now opened by passing a finger downwards through the medial end of the wound into the scrotum, stretching the underdeveloped scrotum over the forefinger until it consists of only dartos muscle and skin. A large curved hand-needle is passed retrogradely through the lowest point of the scrotum upwards to appear in the medial end of the wound. The ends of the suture previously inserted into the gubernacular remnant are threaded through the eye of the needle and the needle then used to pull these ends out through the scrotum and guide the testicle down into the scrotum.

No form of fixation has been attempted in these cases. The 2 ends of the stitch emerging from the scrotum are not tied but are merely cut 2.5 cm below the scrotum (Fig. 3) and covered with a sterile dressing. If there is a tendency for the testicle to retract back up into the groin postoperatively, then as it does so the ends of the stitch will follow, the length protruding from the scrotum becoming shorter or even disappearing altogether. The length of the stitch below the scrotum can be measured on the first postoperative day and on the day of discharge from hospital when it is cut flush with the scrotal skin.

Results

No conclusions about histological or functional results are drawn from this series. Results are judged on the degree of anatomical normality achieved which is an indication of the cosmetic success of the operation. The position of the testicle can be easily observed, and it may be simply described as high scrotal, mid scrotal, or low scrotal in position. It may be described more exactly by measuring its position below the pubic tubercle (Scorer, 1956). Size may be judged in comparison with the scrotal testicle in unilateral cases. Estimation of testicular sensitivity and consistency is more difficult, but the difference between a normally firm and a frankly soft testicle should be readily appreciated. In reporting the results, 4 groups will be discussed according to the position of the undescended testicle.

The Obstructed Testicle

28 testicles were situated in the superficial inguinal pouch. All of these testicles were judged to be of good size and consistency at operation. After mobilisation these testicles could be placed well down in the scrotum with ease. At follow-up all testicles were situated satisfactorily in the scrotum, 23 were in a low scrotal position and 5 were mid scrotal. All lay between 6 and 8 cm below the pubic tubercle. Size, consistency and sensation were judged normal. A satisfactory result was therefore seen in all the testicles in this group.

The Arrested Testicle

(1) *The Emergent Type* (situated at the external inguinal ring). Six out of 7 such testes were in the bottom of the scrotum, 6 cm or more below the pubic tubercle at the follow-up examination were of normal size, consistency and sensation. One testicle, although of normal size, was situated high in the scrotum.

(2) *The Intracanalicular Type*. 12 testicles were found in the inguinal canal at operation, 8 were judged to be of normal size and consistency, but 4 were considered smaller than normal with a softer consistency. At follow-up 5 testicles were in the low scrotal and 4 in the mid-scrotal positions, lying 6 cm or more below the pubic tubercle. One testicle was atrophied and 2 were

in a high scrotal position. Of the 4 testicles considered small at operation, 2 remained small but 2 seemed to attain normal size. In 9 out of 12 cases the result was satisfactory.

(3) *High Inguinal* (situated at the internal inguinal ring). Three testicles were found behind the internal ring and all were of a surprisingly large size. After mobilisation all 3 testicles were left without fixation at the scrotal neck. One testicle descended into a true scrotal position after 1 year. Two testicles remain at the scrotal neck after a shorter period of follow-up.

Discussion

The author believes that emphasis on fixation of the testicle distracts attention from adequate dissection and mobilisation of the cord structures in the region of the internal ring. It has been suggested that if the testicle is not fixed it will retract up into the neck of the scrotum or groin. This seems unlikely since the cremaster muscle will have been destroyed and the mobilised vessels will not be subject to the upward pull of the peritoneum. By the simple measure of leaving the stitch attached to the gubernaculum protruding from the scrotum for 2.5 cm it has been shown that there is no tendency for the testicle to retract upwards. This point having been established, the stitch is now cut flush with the scrotal skin after being used to guide the testicle down into the scrotum.

The results of operation for undescended testicle reported in the literature vary widely. Brunet, De Mowbray and Bishop (1958) reported completely satisfactory results, that is normal size, position and consistency of the testicle, in 65% of operated cases. In 1967 Scorer reviewed a series of 99 patients, 26 of whom had bilaterally undescended testicles. The results were anatomically satisfactory in 80% of cases. As regards size and consistency, however, only 51.4% were judged to be normal. In the present series 44 (88%) of 50 testicles operated upon were completely satisfactory on clinical examination.

Summary

A simple 1-stage operation for unilateral and bilateral undescended testicles is described.

Emphasis is placed on mobilisation of the vessels at and above the internal ring, and no fixation of the testicle is employed, dispensing with the need for incision into the scrotum.

Taking into account the size, consistency, sensitivity and position of the testis, the result was satisfactory both anatomically and cosmetically in 44 out of 50 operations (88%).

I am grateful to Mr A. Gourevitch, Surgeon to the United Birmingham Hospitals, and to Mr A. Rhodes, Surgeon to the Coventry Hospitals, for allowing me to operate on their patients.

Mr H. D. James, Clinical Photographer to the Coventry Hospitals, kindly took the photographs.

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Irrigation at Vasectomy and the onset of "Sterility"

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A recent medico-legal indication has suggested that vasectomy may be considered successful following the failure to demonstrate sperm in a direct film obtained from 2 consecutive semen specimens (Addison, 1972). Previously some surgeons had considered that this decision should only be made after examination of centrifuged semen thereby ensuring every reasonable precaution had been taken (Monro, 1971).

Since it has been reported that irrigation of the vas with sterile water significantly reduces the incidence of positive sperm counts found in centrifuged semen at 12 and 15 weeks after operation (Craft and McQueen, 1972), a study was undertaken to assess whether this technique may shorten the latent time to the onset of "sterility" by examining a direct film of semen as early as 3 and 4 weeks. This communication reports the results of such a study.

Methods

A decision to perform vasectomy on social grounds was made following interview of both husband and wife at a contraceptive clinic and after written consent had been obtained from both partners. All operations were performed under local anaesthesia by one surgeon through bilateral scrotal incisions approximately 0.75 cm in length using a forcep designed to facilitate the procedure (Craft, 1972). The distal cut end of the vas was cannulated with a disposable plastic intravenous cannula and 20 ml sterile water injected under pressure. Approximately 5 cm of vas was then excised.

After the operation the patients were advised to ejaculate as frequently as possible and detailed instructions were given concerning the collection of semen to be examined 3, 4 and 12 weeks later within 3 hours of production. When positive counts were reported on examination of a direct film, further specimens were obtained until 2 consecutive samples were azoospermic.

Semen analyses were performed by examination of both a direct film and a deposit obtained following centrifugation (Craft and McQueen, 1972) using the $\times 40$ objective of a light microscope. At least 10 fields were examined in each instance and sperm were reported as being either present or absent, no account being made of qualitative or quantitative findings.

Results

The results of semen analyses are shown in the Table.

In 36 of the 55 patients no sperm were demonstrable in a direct film made from consecutive specimens at 3 and 4 weeks, *i.e.* the procedure was successful within 1 month of vasectomy in 65% of subjects according to the criteria previously described.

At 12 weeks 11% had occasional non-motile spermatozoa reported. The incidence of positive counts found after centrifugation was not obviously different from assessment of a direct film at 4 and 12 weeks.

No motile sperms were seen in any specimen.

Discussion

Irrigation of the vas with water has been reported to reduce significantly the incidence of positive sperm counts following vasectomy. Craft and McQueen (1972) reported occasional spermatozoa in 34% of control subjects compared with 16% of those having irrigation when centrifuged semen was examined at 12 weeks. The findings of this study confirmed this effect, sperm being found in centrifuged semen in 13% of subjects at this time.

Table

Semen Analysis Following Vasectomy with Irrigation

Time after Operation (wk)	No. of Patients	Sperm Present	
		Direct Film	Centrifuged Deposit
3	55	18 (33%)	25 (45%)
4	55	13 (24%)	15 (27%)
12	52	6 (11%)	7 (13%)

The results suggest that following irrigation there is little advantage in analysing semen in any more detailed manner other than a direct film preparation from 4 weeks after the procedure.

Although Freund and Davis (1969) reported an association between the frequency of ejaculation and the rate of disappearance of spermatozoa, it is suggested that the simple additional expedient of irrigating the vas has obvious advantages. Not only is it likely that fewer patients will have persistent positive sperm counts following vasectomy but two-thirds of subjects will no longer require to take contraceptive precautions for more than 4 weeks after operation.

The operations were undertaken at Kingston Hospital under the auspices of the Kingston Contraceptive Clinic Limited and I am grateful to Mrs Joan Smith and other members of the nursing staff for their assistance and to the members of the Pathology Department for performing the semen analyses.

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CONFERENCE REPORT

The Second International Conference of Voluntary Sterilisation

This conference, sponsored by the Association for Voluntary Sterilisation Inc., met in Geneva from 25th February to 1st March 1973, and was attended by over 350 delegates from 67 countries. This was one of the most efficiently organised international conferences I have attended. The main papers in the mornings were well grouped while the different working party sessions in the afternoons dealt with female and male clinical aspects and with a multiplicity of social, ethical and legal problems.

Male sterilisation was divided into "clinical aspects" and "scientific aspects" but unfortunately it was not possible to attend both workshops. The clinical aspects group was very expertly chaired and reported by Dr Joseph Davis and Dr Sidney Schulman of New York who presented a carefully prepared summary of the problems, together with important questions which had to be answered where possible. The full proceedings will be published in due course. It is interesting to record that of the 19 nations attending the working party dealing with the clinical aspects of male sterilisation—chiefly vasectomy—no European country was represented other than Britain. It is obvious that many legal and ethical problems in Europe are still unresolved.

It was to be expected that the surgical technique workshop would largely be concerned with vasectomy, and although intra- and extra-luminal gadgets were discussed, it was agreed that the primary object was to divide the vas and keep the ends apart. How one did this and which material one used was largely irrelevant. A difference in philosophy between the Americans, British and Australians on the one hand and the developing countries on the other, became obvious during the surgical working party discussions. We were concerned with preoperative counselling of husband and wife, with refinements of technique, with postoperative morbidity or discomfort, with the risks of failure and with the time taken to establish sterility, but the problem in Asia is quite different. They are interested in numbers. We were told that 13,000,000 vasectomies had been performed in India so far, and that the record was 320 operations performed in one day in the railway station in Bombay. With this sort of programme it is obvious that there is no time for counselling or postoperative care or sperm counts. The occasional failure is irrelevant to the main problem. It could be true to say that while we are concerned with controlling the size of our personal families, Asia is concerned with slowing down the increase in her total population. These 2 problems are different. We would not agree to vasectomy being performed by medical auxiliaries but in Asia there could never be sufficient doctors to do this work, and in fact, I think that vasectomy *per se* can have only a marginal effect on the main population problem in the developing countries.

For British urologists the most important statement to emerge from this conference concerned postoperative semen counts, because we are all familiar with the patient who continues to produce a few dead sperms many months after a vasectomy. The working party grasped this nettle and agreed that dead sperms could not fertilise an ovum. They therefore agreed unanimously that the presence of an occasional dead sperm in a fresh semen specimen after 10 to 20 ejaculations was of no significance and that there was no need to continue with semen counts until azoospermia was established. It must be emphasised that the presence of live sperms is quite a different

problem. If this statement is true, and I believe it is, the expense, manpower and time to be saved in this country could be very great indeed. This particular discussion was treated with kindly tolerance by my Asian friends who thought that we were fussing. However, when this statement is recorded in the published conference report, Defence Societies please note.

HOWARD G. HANLEY,
March 1973.

Evaluation of Doxycycline Administration in Patients with Renal Failure and in Normal Subjects

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The potential dangers following the administration of the tetracycline group of antibiotics to patients with normal renal function and more particularly those with renal failure, have recently been stressed; they include a rise in blood urea due to an anti-anabolic effect, impairment of urine-concentrating ability and deterioration in renal function which is often aggravated by salt and water depletion, produced by nausea, vomiting, diarrhoea and an increased urinary sodium excretion (Leading Article, *British Medical Journal*, 1972). Doxycycline however seems to be free of toxic effects in patients with renal failure, although its *in vitro* antibacterial activity is similar to tetracycline and it may also be effective against some strains of staphylococci and escherichia which are resistant to tetracycline. Thus it has been reported that doxycycline shows no anti-anabolic effects (Little and Bailey, 1970; Jacobs and Legrain, 1971). One possible reason for this lack of toxicity is that the serum half-life of doxycycline is not prolonged in severe renal failure and is similar to that in normal subjects (Mérler *et al.*, 1969; Mahon, Wittenberg and Tuffnel, 1970). Because of the importance of these observations, it was decided to try and confirm them, and also to study the long-term effects of doxycycline administration on renal function in normal subjects.

Methods

Serum doxycycline half-life was determined in 6 normal subjects, all male and aged between 20-39 years. Half-life determinations were also made in 8 patients on maintenance haemodialysis, half of whom were male and with an age range of 24-47 years. In 6 of these 8 patients on maintenance haemodialysis, the serum doxycycline half-life was determined on 2 occasions, once during haemodialysis with a Kiil dialyser, and again during a non-dialysis interval. All subjects and patients agreed to the tests after being fully informed of their nature.

The serum half-life was determined over the period of 12-38 hours following a single oral dose of 200 mg of doxycycline. Serum samples were stored at -10°C until assayed. The half-life was calculated by the method of least squares using a computer.

The doxycycline concentration in the serum samples was determined by the large plate cup assay technique, using *Bacillus cereus* var. *mycoides* (NCIB 9231) as the test organism.

In 2 normal volunteers (J. R. C. and K. G. K.), doxycycline was given in a loading dose of 200 mg orally followed by 100 mg orally once a day for 1 month. During this period, blood urea concentration, endogenous creatinine clearance and renal concentrating ability were determined at weekly intervals.

Blood urea concentration and blood and urine creatinine concentrations were determined on a Technicon Mark I Autoanalyser with standard Technicon N-methodology. Renal concentrating ability was assessed by determining the maximum urine osmolality achieved after a combination of 14 hours' overnight dehydration together with 5 units of Pitressin tannate in oil by intramuscular injection. The maximum urine osmolality in normal subjects using this technique is greater than 850 m.osm./kg (unpublished observations). Urine osmolality was determined on an Advanced osmometer.

In 8 patients with varying degrees of chronic renal failure, (not on dialysis treatment), doxycycline was given in a loading dose of 200 mg orally followed by 100 mg orally once a day, for periods

of between 10-15 days. All patients gave their informed consent to these experiments. Blood urea concentration was determined at frequent intervals before and during the administration of doxycycline. In 6 of these 8 patients, ^{51}Cr —EDTA clearances were determined before and at the end of the period of doxycycline administration. The single injection method was used to determine ^{51}Cr —EDTA clearances.

Table I

Serum Doxycycline Half-life in Normal Subjects and Patients on Maintenance Haemodialysis. The Doxycycline Half-life was Determined during a Dialysis Free Interval in the Patients

Subject	Half-life (hours)	Subject	Half-life (hours)
K. K.	19.8	M. N.*	18.7
J. C.	14.9	P. S.	19.0
D. L.	20.3	E. R.	22.7
R. P.	12.4	B. F.	17.7
R. L.	12.7	J. S.	19.6
J. E.	12.7	D. J.	14.3
		A. P.	30.9
		P. C.*	13.3
Mean	15.5	Mean	19.5
Range	12.4-20.3	Range	13.3-30.9
S.D.	3.6	S.D.	5.5

* = Anephric patients.

Results

Doxycycline Half-life in Normal Subjects and in Patients on Maintenance Haemodialysis (Table I)

The mean serum half-life in 6 normal subjects was 15.5 hours. The mean serum half-life in the 8 patients on maintenance haemodialysis was 19.5 hours. Out of the 8 patients on maintenance haemodialysis 2 were anephric, and the remainder had endogenous creatinine clearances of less than 5 ml per minute prior to starting dialysis treatment.

There was no significant difference in the half-life of doxycycline in the normal subjects when compared with the half-life in the patients on dialysis treatment. ($P = 0.114$, Mann-Whitney U Test; $P < 0.2 > 0.1$, parametric t test.)

Effect of Haemodialysis on Serum Doxycycline Half-life (Table II)

In 5 of the 6 maintenance haemodialysis patients, the serum doxycycline half-life was shorter during dialysis than when it was determined during a dialysis free interval. This reduction in half-life was not marked and was not statistically significant although the number of observations was small. ($P = 0.197$, Wilcoxon Matched Pairs Signed Ranks Test; $P < 0.1 > 0.05$, Paired t test.)

Effect of Doxycycline on Renal Function in Two Normal Subjects (Tables III and IV)

Two normal subjects (J. R. C. and K. G. K.) were given doxycycline for 1 month. There was no effect on blood urea concentration, endogenous creatinine clearance or renal concentrating ability. Serum doxycycline levels were estimated weekly immediately before the next dose of doxycycline was due. There was no evidence of accumulation of the drug.

Table II

Serum Doxycycline Half-life (hours) in Maintenance Haemodialysis Patients during and between Dialysis

Subject	No Dialysis	During Dialysis
M. N.*	18.7	13.0
P. S.	19.0	14.0
E. R.	22.7	20.3
J. S.	19.6	11.3
P. C.*	13.3	11.3
B. F.	17.7	40.9
Mean	18.5	18.5
Range	13.3-22.7	11.3-40.9
S.D.	3.2	11.5

* = Anephric patients.

Table III

Effect of Administration of Doxycycline for 1 Month on Renal Function in a Normal Subject J. R. C.

	Control	Week 1	Week 2	Week 3	Week 4
Blood urea mg %	26	42	35	39	41
Creatinine clearance ml/min.	119	125	102	114	133
Concentrating ability max. U. osm. m. osm./kg	910	>1,000	964	936	>1,000
Serum doxycycline μ g/ml	...	1.23	1.27	1.25	1.83

Table IV

Effect of Administration of Doxycycline for 1 Month on Renal Function in a Normal Subject K. G. K.

	Control	Week 1	Week 2	Week 3	Week 4
Blood urea mg %	30	54	37	35	34
Creatinine clearance ml/min.	154	154	140	129	181
Concentrating ability max. U. osm. m. osm./kg	951	>1,000	923	989	963
Serum doxycycline μ g/ml	...	1.56	0.84	0.67	0.66

Effect of Doxycycline Administration on Blood Urea Concentration in Patients with Chronic Renal Failure (Table V)

There was no evidence of an anti-anabolic effect during the administration of doxycycline in normal doses for periods of 10-15 days in 8 patients with varying degrees of chronic renal failure. There was in fact, an overall tendency for the blood urea to fall slightly during the period of doxycycline administration as shown by Analysis of Variance and the paired *t* test ($P < 0.05 > 0.02$). There was, in addition, a slight overall tendency for the ^{51}Cr —EDTA clearance to rise during the period of doxycycline administration ($P < 0.05 > 0.02$, paired *t* test).

Table V

Effect of Doxycycline Administration on Blood Urea Concentration in Patients with Chronic Renal Failure

Subject	Sex	Age	Mean Blood Urea (mg %) and S.D. in parentheses		^{51}Cr —EDTA Clearance (ml/min.)	
			Before	After	Before	After
K. W.	F	81	49 (1.4)	61 (5.8)	68.5	73.7
D. I.	M	55	115 (4.1)	121 (4.0)	10.8	11.2
F. H.	M	61	175 (10.1)	173 (6.6)	4.2	5.8
M. M.	F	67	73 (1.0)	71 (7.7)	25.8	22.1
L. C.	M	24	181 (3.2)	146 (11.8)	7.9	9.2
S. B.	M	67	152 (0)	145 (5.1)	16.0	15.7
W. H.	M	74	74 (7.2)	47 (7.0)	...	53*
M. C.	F	55	107 (21.7)	81 (34.6)	...	10.0

* Endogenous creatinine clearance.

Discussion

The mean serum half-life of doxycycline in patients with normal renal function has been reported as 18 hours (Mahon, Wittenberg and Tuffnel, 1970) and 22 hours (Fabre, Pitton and Kunz, 1966) and similar values have been reported in patients with severe renal failure (Mérinet *et al.*, 1969; Mahnon, Wittenberg and Tuffnel, 1970). The present study confirms these findings, there being no significant difference in the half-life in the normal subjects (mean 15.5 hours) and the half-life in the patients on maintenance haemodialysis (mean 19.5 hours). During haemodialysis with a Kiil dialyser, there was a tendency for the half-life to be shorter but the differences were not statistically significant although the number of observations was small. In practical terms, these results suggest that there is no need for modification of the dosage of doxycycline in the presence of severe renal failure and no adjustment is necessary during haemodialysis with a Kiil dialyser.

It has also been reported that the administration of doxycycline to patients with renal failure does not lead to a rise in blood urea concentration (Little and Bailey, 1970), implying that doxycycline unlike other members of the tetracycline group of antibiotics does not have an anti-anabolic effect. In addition, it has been reported that urinary nitrogen excretion is not increased during doxycycline administration to patients with renal failure, (Jacobs and Legrain, 1971). The present study confirms the observation that doxycycline administration to patients with chronic renal failure does not lead to rises in blood urea concentration. There was on the contrary a tendency for the blood urea concentration to fall. The explanation for this is not clear, but may be partly related to the tendency for the ^{51}Cr —EDTA clearance to rise a little during the period of study.

Anti-anabolic effects and nephrotoxic effects may be produced by drugs of the tetracycline

group in subjects with normal renal function (Shils, 1963; Roth *et al.*, 1967). Impairment of renal concentrating ability has been reported in normal subjects given demethyl-chlortetracycline orally (Roth *et al.*, 1967). In the present study, 2 volunteers given doxycycline orally for 1 month showed no change in blood urea concentration, endogenous creatinine clearance or renal concentrating ability.

Doxycycline by virtue of its lack of nephrotoxicity and absence of anti-anabolic effects, would seem therefore to be particularly valuable when a broad spectrum antibiotic is needed in patients with renal failure.

Summary

The biological half-life of doxycycline in serum was determined in 6 normal subjects and in 8 patients on maintenance haemodialysis. There was no significant difference in the half-life in the 2 groups. In 6 patients on maintenance haemodialysis the half-life of doxycycline was determined both during and between haemodialysis. There was a tendency for the half-life to be shorter during haemodialysis, but the differences were not statistically significant. It is concluded that no adjustment of dosage is required when doxycycline is employed in patients with severe renal failure, whether they are undergoing haemodialysis or not.

Renal function was studied in 2 normal subjects who were given doxycycline in normal doses for 1 month. During this period there was no change in blood urea concentration, endogenous creatinine clearance or renal concentrating ability.

Doxycycline was administered in normal doses to 8 patients with varying degrees of chronic renal failure for periods varying from 10 to 15 days. There was no evidence that doxycycline had any anti-anabolic effect and there was no evidence of nephrotoxicity. No toxic effects were noted in any of the patients studied.

Doxycycline is therefore of particular value when a broad spectrum antibiotic is required in patients with renal failure.

We are grateful to Dr R. F. Jewkes and Miss B. E. Jones of the Department of Nuclear Medicine, Charing Cross Hospital (Fulham) for the ^{51}Cr —EDTA clearance measurements. Thanks are due to Dr J. Daly and the staff of the Department of Biochemistry, Fulham Hospital for blood urea and creatinine determinations. We wish to thank Sister M. Greatbatch and the staff of the Maintenance Haemodialysis Unit, Charing Cross Hospital (Fulham) who collected some of the blood samples. Dr F. J. A. Bateman, Pfizer Ltd. kindly supplied the doxycycline used in the study.

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Short Case Reports

Intrarenal Arterio-venous Malformation

Renal arterio-venous malformations of congenital origin are rare (Twigg, Pradham and Perloff, 1962; Gunterberg, 1968; Elkin, 1971). Emmett and Witten (1971) state that only 25 cases of congenital renal arterio-venous malformation had been reported in the literature.

Case Report. J. K., a 69-year-old widow, had intermittent haematuria, with some dysuria of 2 days' duration. She had had 1 episode of haematuria 5 weeks previously. She complained of a central abdominal ache, weight loss and anorexia. On examination she was pale, with regular pulse and blood pressure 150/90 mm Hg. There was a thrill in the left abdomen and a very loud bruit.

The preliminary film before intravenous urography showed patchy calcification, with 2 ring shadows, lying within the left renal shadow. Following injection of contrast, the right renal appearances were normal. On the left side a nephrogram was seen at 10 minutes, with lateral renal displacement (Fig. 1). The calcification lay over the distal renal pelvis, extending from the 6 cm to the 12 cm tomographic cuts, which also demonstrated excretion from the upper left calyceal group. A 5 hours' film showed that the calcified mass indented the pelvis anteriorly.

The chest film showed cardiomegaly and pulmonary venous hypertension. Abdominal aortography demonstrated a small normal left renal artery and arising just superior to this a large abnormal artery (Fig. 2, A) which ran a tortuous course to the left lower pole to enter an abnormal complex of vessels drained by a very large vein (Fig. 2, B).

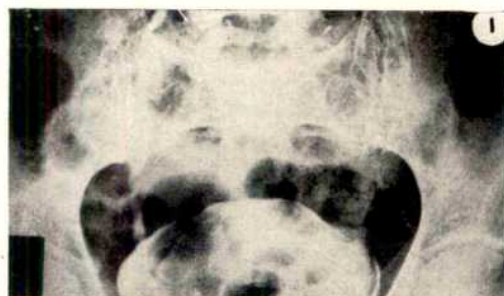
Immediately following aortography, the patient was transferred to theatre for left nephrectomy. Examination of the specimen showed the abnormal artery was 1.3 cm, the vein 2 cm, in diameter. There was no evidence of infection or hypernephroma. The appearances were "those of a developmental abnormality—an arterio-venous fistula with aneurysm".

I wish to thank Mr S. F. Soutar, surgeon, and Dr W.

Fig. 1. I.V. Urogram. Normal right collecting system. The left kidney is displaced laterally, with calcification over region of distal renal pelvis. Filling defects in bladder accepted as blood clot.

Fig. 2A. Main stream aortogram showing normal left renal artery and abnormal renal artery proximal to it.

Fig. 2B. Venous phase of aortogram, with large vein draining into the large inferior vena cava.



Guthrie, pathologist, for permission to present this case.

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Urethral Coitus in a Case of Vaginal Agenesis

A 22-year-old woman complained of dribbling urine since her marriage 3 years previously. Initially penetration by the penis had not been possible, but within 3 days it was achieved. The severe pain and bleeding which it caused were dismissed by the couple as normal, and intercourse took place several times a week. The patient developed incontinence of urine, worst immediately after intercourse, but she had no other urinary symptoms. She appeared a normal female (confirmed by the chromosomal pattern of a buccal smear) but there was no vagina. The urethra easily admitted 3 fingers. No uterus or cervix could be felt per rectum or per urethram. The urine yielded a mixed culture of *Klebsiella*, *E. Coli* and *Proteus*. I.V.P. was normal. The vagina was reconstructed from an isolated loop of colon, and the urethra and bladder neck were plicated. The urinary infection cleared up after a course of chloramphenicol and later of mandelamine. The urinary incontinence ceased, although a postoperative cystogram showed that the bladder neck was still markedly dilated.

Of 16 cases of urethral coitus reported (including the present case) only 2 of them had vaginal agenesis.

P. P. TANEJA, D. HEERA, S. M. GULATI and N. K. GROVER, New Delhi, India.



Postoperative cystogram showing wide bladder neck and urethra with vesico-ureteric, reflux on left side.

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Book Reviews

Abrégé d'Urologie. By JEAN CIBERT, JAKES CIBERT and REZA MASSOUMI MOHADJER. Pp. x + 313, with illustrations. Paris: Masson et Cie. 1972.

An excellent book, written specifically for the (French) senior student and beginner in Urology, its pages pruned of the fanciful and fruitless. It is a distillation of a lifetime's thoughtful experience compacted into 308 pages. Some might have wished for a more leisured and expansive volume from Professor Cibert as his time at the Edouard Heriot draws to an end. More senior urologists will turn to his publications over the quarter century in which he pioneered so much. It is typical of the man that as a teacher he sees the needs of the young men as his first and last responsibility. So this is a fitting book to mark the end of an epoch in the history of Pavilion V.

J. P. W.

Advances in Nephrology. From the Necker Hospital. Volume 2. Edited by JEAN HAMBURGER, JEAN CROSNIER and MORTON H. MAXWELL. Pp. 291, 73 illustrations. Chicago: Year Book Publishers (Distributed by Lloyd Luke, London). Price, £10.75.

This is the second of a series of annual volumes based on the Advances in Nephrology conferences at Necker, the Mecca of French nephrology. They are intended to give a summary of growing points in the subject more up-to-date than is possible in textbooks but more comprehensive than journal reviews can hope to be. The first volume certainly achieved that aim and most of the present volume also succeeds in doing so. If the standard can be maintained and the publication time kept short, most renal physicians and pathologists will find that they cannot afford to be without this series on their bookshelves though they will wince at the price.

This volume contains a very full review of the structure, function and biochemical characteristics of the basement membrane, occupying nearly half the book. There are also some chapters in the second main section which cover the subject so well that they will be automatically quoted by future reviewers—the chapter on extracapillary ("malignant") glomerulonephritis and Peters' review of diuretics, for instance. However there are other sections which fall between two stools, being neither simple enough to give a quick insight to the uninitiated, nor comprehensive enough to help the worker in the field. Much of the section on artificial membranes attracts this criticism.

There are a few chapters which might interest the practising urologist. Anyone who uses diuretics ought to read van Ypersele's concise account of the metabolic abnormalities they produce, and the urologist who wants to discuss renal failure on level terms with his medical colleagues must know about the "trade-off hypothesis" of Bricker. However if surgical urology is your main interest in life, it is a book to browse through in the library, not the obvious next choice for your personal collection.

D. N. S. K.

Current Controversies in Urologic Management. Edited by R. SCOTT. Pp. xxi + 399 with illustrations. London: W. B. Saunders Co. 1972. Price £7.50.

There is as yet no final solution to many problems in surgery. The result is a divergence of opinion which may make it difficult to select a particular method of treatment. With experience, the surgeon's opinions harden, and perhaps become too rigid. The clinician must be prepared to re-examine his methods and to be willing to change them if they are found wanting.

This book will compel reflection on the validity of the surgeon's opinions. It is a unique and fascinating book which deserves to be read from cover to cover by all urologists. The layout is unusual—21 topics are discussed by 58 contributors. A specific problem is outlined by the editors, followed by 2 or more essays in which each author puts his case for a particular method of management. These are followed by a brief editorial comment. A wide range of subjects is covered, and in spite of the large number of contributors the result is a book of remarkably even standard, clearly and concisely argued, yet very easy to read.

One of the most interesting aspects of this book is the undercurrent of agreement on basic principles which runs throughout most of the essays. Although some views are apparently diametrically opposed and are cogently argued, a rigidly dogmatic approach has been avoided. The result is a book which encourages flexibility and reasoned argument. The reader will find how a patient can be managed, or how an operation can be performed—it will not give the answer to "How should this be done?"

A book of this nature inevitably has some disadvantages. Only a limited number of opinions can be discussed. It would have been interesting to see included an essay opposing the use of radical prostatectomy for carcinoma, or opposing radical lymphadenectomy for germinal tumours of the testis. Management of the traumatic cord bladder is discussed in 2 essays—Treatment without Diversion, by Comarr, by Vesicostomy by Lapedes. Although there is some mention of the numerous other procedures which are available, vesicostomy is perhaps a curious choice to make as the principal subject for discussion in contrast to Comarr's essay. Editorial comment at the end of each section is benign, often brief. The authors have presented their case; sharper criticism would often be welcome, although, as the editors themselves observe, on occasions the choice is so open that the reader must weigh for himself the arguments that are presented.

These are minor criticisms—they amount to a wish that this book could be longer. "Current Controversies" is a welcome addition to the urological bookshelf, and it is to be hoped that it is the forerunner of a new concept in medical literature.

D. M. E.

CONFERENCES AND COURSES

An INTERNATIONAL SYMPOSIUM ON PROBLEMS OF PHENACETIN ABUSE will be held in Vienna, 29th-30th November 1973.

Please address enquiries to:

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UROLOGICAL SOCIETY OF AUSTRALASIA

The 27th Annual Meeting of the Urological Society of Australasia will be held in Melbourne from 3rd to 7th March 1974.

Further information may be obtained from:

Dr David Yoffa, FRACS,
12 Collins Street,
Melbourne 3000,
Australia.

Errata. In the last issue of the *Journal* (Vol. 45, No. 3, June 1973) on page 303 line 10 (Y.R.) column 6 should have read U+I—; line 26 (D.C.) column 7 should have read U—I—.

ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

Acta Urologica Belgica

By VICTOR LANE

"Primary Tumours of the Ureter and Renal Pelvis." J. BRENEZ and PH. HAWOTTE. (1972, 40, 505-532.)—Although based on a series of only 13 cases, a full well illustrated account is given of these neoplasms. It is interesting that the authors consider that leukoplakia of the ureter is a pre-malignant condition.

"Leiomyosarcoma of the Ureter." Y. GOFFIN and P. VANWELKENHUYZEN. (1972, 40, 533-536.)—This is claimed to be the eleventh case of this very malignant tumour to be reported. The neoplasm was inoperable and a palliative nephrectomy only was possible. These neoplasms are not radio-sensitive.

Percutaneous Puncture of the Kidney—Radiological Possibilities." L. BAERT and G. BARBE. (1972, 40, 548-565.)—The technique is discussed and excellent illustrations show the value of this method in the diagnosis of renal cysts and neoplasms of the renal pelvis and ureter, when the intravenous urogram showed no function and retrograde catheterisation was not possible.

"Ureteroceles." C. C. SCHULMAN. (1972, 40, 687-719.)—Reviewing 131 cases of ureterocele, this paper gives a full account of the subject, which is beautifully illustrated by line drawings and radiographs.

"Percutaneous Puncture of Renal Cysts." W. GREGOIR, M. WEISER, E. HALLEMANS and C. C. SCHULMAN. (1972, 40, 745-752.)—This procedure is recommended as a safe and accurate means of distinguishing between renal cysts and tumours; in particular, it avoids the risks associated with arteriography. 30 cysts were aspirated and the diagnosis confirmed with certainty in 28 cases. Occasionally, the cyst does not refill after it has been emptied completely.

"Xanthogranulomatous Pyelonephritis." J. P. HANS, E. DE BACKER, T. GRATTON-DESART and H. Q. MALDAGUE-PHAM. (1972, 40, 753-763.)—Four cases are described and the clinical picture and pathology discussed.

"Ureteric Function after High Uretero-Vesical Reimplantation." H. MELCHIOR, S. LYMBERPOULOS, B. TERHORST and W. LUTZEYER. (1972, 40, 778-783.)—The bladder having been mobilised and "hitched" to the psoas, if necessary, the ureter is implanted through a submucosal tunnel and splinted. This operation has given satisfactory results in 25 patients—in only 1 patient did a postoperative reflux develop and only 1 had a postoperative stenosis.

"Co-existence of Cyst and Neoplasm in the same Kidney." E. HALLEMANS and C. C. SCHULMAN. (1972, 40, 818-824.)—It is stated that 2% of cases of renal cyst are associated with a tumour in the same kidney—

a classification of 5 different types of co-existence is given and methods of diagnosis are discussed.

American Journal of Roentgenology

By M. H. DEVEREUX

"Sigmoido-vesical Fistula Secondary to Diverticulitis." J. J. CANCELMO, Jr., J. L. ESHLEMAN, R. C. UHLMAN and N. F. VIEK. (1972, 115, 378-383.)—Four cases of vesico-colic fistula are presented. All had cystitis, faecaluria and pneumaturia and these symptoms appear to be more valuable in making a diagnosis than urological investigations. The fistula is more likely to be demonstrated by barium enema than by urography, cystography or cystoscopy. All cases were treated by 3-stage resections and closure.

"Pelvic Lipomatosis: A Roentgenographic Diagnosis." ALBERT A. MOSS, ROBERT E. CLARK, HENRY I. GOLDBERG and H. WALTER PEPPER. (1972, 115, 411-419.)—Ten cases of this rare condition are added to the 20 cases previously reported. Only 1 case has been reported in a female. There are no specific clinical features. X-rays show increased lucency in the bony pelvis and urography shows marked and sometimes bizarre distortion of the bladder associated with medial displacement of the ureters in the pelvis.

"Detection of Vesico-ureteral Reflux with Radionuclide Cystography. A Comparison Study with Roentgenographic Cystography." J. J. CONWAY, L. R. KING, A. B. BELMAN and T. THORSON. (1972, 115, 720-727.)—Concern over the radiation exposure of children having multiple cystograms led to this study of radionuclide cystography using ^{99m}Tc pertechnetate with the gamma camera. 100 children were studied and radionuclide cystography was found to be more reliable than routine cystography in detecting significant vesico-ureteric reflux. The dose of radiation to the gonads was reduced by 50-100 times. The main disadvantage is that little information can be obtained about the bladder or urethra.

"Interstitial Cell Carcinoma of the Testis. A Case Report." J. E. LIVESAY, H. E. BRANCH and W. L. EATON. (1972, 115, 728-731.)—The 12th case of malignant interstitial cell carcinoma of the testis to be reported is presented. The patient developed bony metastases 6 years after removal of the primary testicular tumour. There was no significant response to radiotherapy or chemotherapy.

"Ultrasonic Evaluation of Masses in Pediatric Patients." B. B. GOLDBERG, MARIE A. CAPITANIO and J. A. KIRKPATRICK. (116, No. 3, 677-684.)—This paper reports the use of ultrasound as a diagnostic aid in abdominal masses in childhood. From the point of view of renal masses ultrasound provides a

simple means of distinguishing cystic from solid swellings.

By B. H. PAGE

"Compensatory Renal Hypertrophy: Absence *in Utero* and Development in Early Life." I. LAUFER and N. T. GRISCOM. (1971, 113, 464-467.)—The authors are radiologists from Boston, Mass. They studied the records of 27 patients with unilateral cystic dysplastic kidneys in whom urography had been done within the first two months of life. All the patients subsequently underwent excision of the affected kidney shortly after the initial urogram was taken. The size of the healthy kidney in every case was within normal limits at birth. Subsequently periodic urograms were done up to the age of 13 years and the radiographic size of the kidney was plotted on a curve against time. This curve was compared with Hodson's curve of the growth of kidneys having a normally functioning partner. The result showed that at birth the size of a kidney having a functionless partner was normal, but that it then grew more rapidly so that by the end of the first year of extra-uterine life the volume of the solitary kidney was equal to the combined volume of both kidneys in a normal child. The authors maintain that the actual removal of the multicystic kidney played no part in this development because no junctioning tissue was removed. They adduce as evidence 2 cases (not in their main series) in which the excision was delayed for 11 months and 24 years respectively and in both cases the functioning kidney had already reached a size comparable with the cases in which the functionless kidney had been removed shortly after birth. The homeostatic function of the placenta is the factor restraining overgrowth of a solitary functioning kidney *in utero*.

"Renal Pseudotumours due to Ectopic Accessory Renal Arteries: the Angiographic Diagnosis." M. M. KYAW and H. NEWMAN. (1971, 113, 443-446.)—This paper is from the Department of Radiology of the Letterman Hospital, San Francisco. The authors describe 2 cases in which the intravenous urogram suggested a renal tumour because of a localised enlargement of the lower pole of the kidney, in 1 case associated with deformity of the renal pelvis adjacent to the enlargement. Arteriography showed that the localised enlargement was supplied by accessory arteries but there was no pathological circulation. Nephrotomography also revealed that the enlargement consisted of normal renal parenchyma. In 1 case the enlargement was associated with malrotation of the kidney affecting the renal pelvis but not the calices on that side. In the opposite kidney the calices were also malrotated so that the diagnosis of malrotation was obvious at the outset. The authors suggest that malrotation may be caused by the tethering effect of accessory vessels.

"Optimum Dose in Excretory Urography." H. W. FISCHER, N. J. H. ROTHFIELD and J. D. CARR. (1971, 113, 423-426.)—Three radiologists from the University of Michigan, Ann Arbor and a nearby hospital (Wayne County) studied the effect of varying concentrations of contrast medium on the quality of the films in relation to clarity of visualisation of calices and pelvis and to distension of calices. The subjects were volunteers with normal renal function and each volunteer was given 3 separate pyelograms

at intervals of 5-10 days, each pyelogram with a different dose of medium. The comparisons were made between the effects of the various doses in the same individual, thus reducing errors due to variation in renal function, state of hydration, subject's size and surface area etc. The comparisons were made by observers not having knowledge of the dose of contrast medium. The conclusion was that the optimum dose of 50% sodium diatrizoate was 1 ml/kg body weight. Increase of concentration above this level brought no further improvement and sometimes a deterioration in quality of definition.

"Milk of Calcium in the Kidney." R. L. MURRAY. (1971, 113, 455-459.)—The author is from Roanoke, Virginia. He describes 4 cases in which milk of calcium was demonstrated in the kidney and he makes the following points. By its nature milk of calcium can only show its characteristic horizon when examined with a horizontal beam of X-rays, whereas in routine renal radiography a vertical beam is used. The vertical beam image for milk of calcium does however have some fairly characteristic features. In the first place the shadow is in the periphery of the kidney as the calcium is in a calyceal cyst and not in the main pelvicalyceal system. Stones in the pelvis or calyces, except when very small, are moulded more or less to the shape of these structures, whereas milk of calcium projects a round shadow even when it is fairly large. Size for size the shadow of milk of calcium is less dense than that of most stones. Finally the edges of the shadow are rather blurred and ill defined compared with the density of the centre. There is also an important clinical consideration, namely that milk of calcium does not cause symptoms and the urinary tract is normal apart from the cyst and its contents.

By JOHN D. TAYLOR

"Carcinoma of the Female Urethra." C. G. TAGGART, J. R. CASTRO and F. N. RUTLEDGE. (1972, 114, 145-151.)—This study from the M. D. Anderson Hospital, Houston covered 37 cases between 1951 and 1968 of which 33 were treated by irradiation. Localized anterior urethral disease is effectively treated by interstitial implantation of radium needles. Advanced cases, especially where there is posterior urethral and bladder neck involvement are best treated by a combination of external irradiation and implantation by the open bladder technique. Urinary function is good with local control of the tumour.

"Hyperbaric Radiation Therapy." HENRY P. PLENK. (1972, 114, 152-157.)—40 patients with carcinoma of the bladder were randomly selected for irradiation either under conditions of hyperbaric oxygen or the normal atmosphere. There was no significant statistical difference in the number of survivors, but the duration of survival was longer in the hyperbaric group.

Annals of Surgery

By J. E. A. WICKHAM

"The Fate of Patients After Renal Transplantation, Graft Rejection, and Retransplantation." S. L.

KOUNTZ and F. O. BELZER. (1972, 176, 509-520).—This paper describes the fate of 403 renal transplants which had been performed on 336 patients at the University of California Medical Center, over a 9-year period. The overall mortality in this series was 21.8%. It discusses patient survival and adds that it was entirely independent of the donor kidney relationship. Survival was 100% in 32 HL-A identical sibling pairs which is probably the best figure reported. There is no statistical difference after 2 years in the graft survival in HL-A non-identical siblings, parents to children or cadaver donors. It is also noted that immunosuppressive drugs have not improved the survival of grafts from related donors during the past 5 years, or of cadaver grafts in the last 3. The authors point out that since graft survival has not improved despite increased experience with immunosuppressive techniques the only way to improve transplant figures is to perform more retransplants. A policy of retransplanting patients has been carried out successfully and within the last 18 months 81% of patients are regarded as having been successfully treated by employing a retransplantation regime.

"Effect of Rabbit ALG on Cadaver Kidney Transplant Survival." R. C. DAVIS, D. C. NABSETH, C. A. OLSSON, B. A. IDELSON, G. W. SCHMITT and J. A. MANNICK. (1972, 176, 521-527).—This paper reviews the effect of giving rabbit antihuman ALG in addition to conventional immunosuppressive therapy to 39 consecutive cadaver transplant recipients. One year transplant survival in this group of patients was 80%. Only one-third of these patients had any clinically detectable acute rejection episodes. Histological and clinical evidence of chronic rejection can be seen in only 3 transplants of the patients in this series. 16 of the patients reached the 2-year interval with good renal function. The 2-year transplant survival rate is 67%. Subcutaneously administered rabbit ALG in a dose of 75-90 mg was administered by subcutaneous injection on alternate days for 5 doses beginning at the time of transplantation. ALG was an antihuman thymocyte globulin raised in rabbits.

"Induction of Immunological Tolerance to Allogeneic Tissues in the Canine Species." F. T. RAPAPORT, K. WATANABE, M. MATSUYAMA, F. D. CANNON, N. MOLLEN, D. A. BLUMENSTOCK and J. W. FERREBEE. (1972, 176, 529-537).—This paper reports the results of a series of experiments on a selectively bred colony of dogs with near DL-A compatibility. Bone marrow obtained from perspective selected DL-A identical donors was transplanted to supraethally irradiated dogs of same DL-A type. Transplants in these animals have survived satisfactorily for periods ranging from 285 to 619 days. Renal allografts were then obtained from the specific donor of the marrow and transplanted into the bilaterally nephrectomised irradiated recipient. In these operations there has been good maintenance of the transplanted kidneys in these dogs for periods ranging from 161 to 556 days. The renal function of these animals appears to be normal. Animals reject the skin graft from unrelated dogs in a perfectly normal manner. This paper is an interesting report on the development of immunological tolerance to allogeneic tissues in the dog. Its relation to human renal transplantation seems a little obscure at the moment.

"Testicular Complications Following Renal Transplantation." I. PENN, G. MACKIE, C. G. HALGRIMSON and T. E. STARZL. (1972, 176, 697-699).—This paper reports a series of 86 male patients who underwent 94 renal homotransplantations through inguinal incisions with division of the spermatic cord to facilitate exposure. Late review of these patients demonstrated that 75% of them had developed either hydrocele, acute necrosis, atrophy or recurrent attacks of pain in the associated testis. Many of the lesions were asymptomatic and the patients were unaware of their existence but it was felt that this degree of morbidity was enough to disqualify routine division of the spermatic cord during renal transplantation.

"Operative Treatment of Renovascular Hypertension." B. NERSTROM and H. C. ENGELL. (1972, 176, 590-596).—This paper reports the results of direct surgery in a series of 60 patients operated on for renovascular hypertension. The commonest indication for this operation was fibromuscular hyperplasia in young patients and atheromatous plaques in middle-age patients. There were 3 deaths in this series. 47 of the 60 patients had been followed for an average of 27 months and 85% were normotensive or markedly improved. None of the 7 patients who did not improve had deteriorated. The diastolic blood pressure taken at 2 weeks postoperative was regarded as the most significant prognostic indicator of success or failure. Patients whose diastolic blood pressure was less than 100 mm of mercury at this time usually became normotensive or showed marked improvement. Those patients with blood pressures over this level usually failed to maintain their initial improvement. This paper seems to represent the better end of the spectrum, of patients treated by operative surgery for renovascular hypertension.

Archivio Italiano di Urologia e Nefrologia

By J. MAGRI

"Experimental Study into the Histopathological and Functional Changes in the Kidney during Treatment with Heterologous Antilymphocytic Serum." V. FRIZZI, G. M. CAPUZZO and L. GIRELLI. (1971, 44, 31-55).—In this investigation from Padova, the animals used were CBA strain mice and the antilymphocytic serum obtained from New Zealand rabbits. The controls included 9 untreated mice and 36 mice treated with normal rabbit serum and a further 36 treated with rabbit ALS. The animals in the last 2 groups were subdivided into 5 equivalent subgroups which received comparable doses of ALS and were killed after varying intervals to provide histological material. In addition, a further 30 mice were treated with normal rabbit serum and ALS to serve for biochemical assessment of renal function. The structural changes noted were restricted to the glomerular basement membrane which showed areas of localised or diffuse swelling alternating with areas of apparent rupture of the membrane. There was an absence of leucocyte infiltration and proliferative epithelial changes, and the picture resembled that seen in chronic glomerulonephritis (Ellis type II). The biochemical investigation failed to show any changes in blood urea levels and no haematuria was detected. Proteinuria was however a prominent feature and varied directly with the dose of ALS. The changes described were

present mainly in the mice treated with ALS, less so in those treated with normal rabbit serum and none at all in the untreated group.

"Transrectal Needle Biopsy of the Prostate." V. MAFFEIS and D. ROTTICHERI. (1971, 44, 79-92).—This paper from Bergamo reports on 80 transrectal prostatic biopsies carried out with the "Travenol" needle. Of these, 25 were reported as carcinoma. The only complication noted was haematuria in 9 cases which cleared spontaneously within 48 hours.

"High-Dose Intravenous Urography in Renal Failure." C. NOE. (1970, 43, 281).—High dose urography together with routine tests of renal function were carried out in 95 patients with renal failure, due to obstructive pathology in 25, and to acute or chronic parenchymal disease in 70, to establish the advantages as well as the limitations of the investigation, and to ascertain whether any additional permanent renal damage may result.

With creatinine values up to 2 mg %, creatinine clearances of 40 ml/min, urea levels up to 80 mg % and urine osmolality of 400 mOsm/l, detail of the renal parenchyma, pelvi-calycal system and the renal tract generally was obtainable in all cases.

With values of 5 mg %, 20 ml/min, 120 mg % and 160 mOsm/l respectively, sufficient detail was elicited in about half the cases. With creatinine and urea levels in excess of the above valid information was forthcoming in about 30% of cases.

In general, obstructive cases showed up better by virtue of the size of the distended urinary tract. Renal function was found to be depressed after high-dose urography, but returned to pre-infusion state within 15 days.

"Treatment of Haematuria after Renal Biopsy with Adrenochrome Monosemicarbazone." C. GROSSI. (1970, 43, 296).—26 patients who underwent renal biopsy with Vim-Silverman needle (Franklin modification) had estimations done of RBC loss in 48 hours. In 11 patients, 50 mg of adrenochrome monosemicarbazone (a haemostatic agent) were given intravenously in 500 ml of 10% glucose solution immediately after biopsy. The average blood loss in these patients (140×10^6 RBC) was significantly lower than in the control group (342×10^6) ($P = 0.05$). The agent used is thought to increase the tone of the capillaries and pre-capillary vessels rather than produce true vasoconstriction.

Archivos Espanoles de Urologia

By C. A. C. CHARLTON

"The Gammacamera with Strontium in the Diagnosis of Metastasis in Carcinoma of the Prostate." E. GARCIA DE LA PENA, J. A. SANCHEZ MARTIN, J. LINAZASORO and L. CIFUENTES DELATTE. (1972, 25, 383-408).—The authors discussed the different isotopes used in studying changes in bone; and thence the use of ^{85}Sr in cancer of the prostate. The indications for using this technique are primarily to establish the absence of metastases in bone when radical prostatic surgery is proposed. Other indications are in patients with carcinoma of the prostate who have bone pain and either doubtful or absent X-ray changes present; further examination of lesions situated in bone where better definition is

difficult as in the sternum and scapula, to improve localisation of a lesion for the purpose of biopsy or radiotherapy etc.

"Renal Cryo-surgery." W. LUTZEYER and S. LYMBEROPOULOS. (1972, 25, 373-382).—A cryo-scalpel has been developed, the cutting edge being steel, and the cooling chamber made of silver. Liquid nitrogen is conveyed to the knife which is vapourised in the chamber, lowering the temperature to -180°C in 10 seconds. This temperature is maintained for 30 to 45 seconds, permitting sectioning of the renal parenchyma (without renal artery occlusion) with virtually complete haemostasis. The coagulation induced extends for 2 to 3 mm in depth. The larger vessels are easily identified, clipped and tied in the usual manner. The resulting scar shows a minimal inflammatory reaction on histological examination. The knife is heated by a small coil, and the temperature returns to 0°C within 6 seconds.

This technique permits conservative renal surgery to be undertaken, with particular reference to calculous disease and partial nephrectomy for tuberculosis and non-functioning halves of duplex systems. Many operations on animals and 9 on humans have been undertaken, with highly satisfactory results.

The Australian and New Zealand Journal of Surgery

By H. H. PEARSON

"The Morphology of Congenital Dilatation of the Ureter: Intrinsic Ureteral Lesions." L. J. CUSSEN. (1971, 41, 185-194).—From the Royal Children's Hospital Research Foundation, Melbourne, the author carried out detailed studies of intrinsic ureteral lesions producing congenital dilatation of the ureter. In 129 (88%) of 147 ureters dissected, measured, fixed and studied there was evidence of muscular hypertrophy and hyperplasia in the wall of the proximal dilated portion of the ureter and these all revealed an obstructive lesion. In the remaining 18 ureters (12%) there was no evidence of increase in size or population of smooth muscle cells in the ureteral wall and no obstructive lesion was demonstrable. He classified the dilated ureters into 4 types with several sub-types: (1) Atresia; (2) Stenosis, (a) Stricture, (b) Segmental Stenosis, (c) Serpiginous Stenosis, (d) Shelving Stenosis; (3) Valve, (a) With ureteral stenosis, (b) With no stenosis; (4) Non-obstructive dilatation. The author then goes on to present examples and discuss the various types and sub-types and their incidence. He considers this to be a sound morphological classification, the article is very well illustrated and he points out the value of such a classification in determining the need for and type of surgery indicated.

"Stenotic Ureterocele." N. SUBBLAH and DOUGLAS STEPHENS. (1972, 41, 257-263).—The authors from the Surgical Research Unit at the Royal Children's Hospital, Melbourne, describe 26 stenotic ureteroceles occurring in 8 male and 13 female children. The stenotic ureterocele, localised totally within the bladder, comprised 42% of all types of 61 ureteroceles. 15 occurred in single ureters in 10 patients, 5 being bilateral and 11 were located on the ectopic ureter of a double ureter system. Infection caused the presenting symptoms in 11 of 19 patients. The radio-

graphic features were most commonly a Basal Dome-like or rounded filling defect with or without the "halo" in the bladder, and on voiding the ureterocele prolapsed into the urethra in 2 patients. Reflux did not occur into the ureterocele. Histological examination revealed a graduation from full muscle coat with or without hypertrophy to gross deficiency of muscle. The shape was considered to be developmental and only in part obstructive in origin. Enlargement of the orifice was effective in 7 out of 9 ureteroceles, mild reflux occurring postoperatively in 2. Trans-urethral enlargement of the orifice they considered indicated if the orifice and the presence of peristalsis had been identified at cystoscopy.

"Urine Cytology and Primary Carcinoma of the Renal Pelvis and Ureter." T. H. CULLEN, R. R. POPHAM and H. J. VOSS. (1972, 41, 230-236.)—The authors from the Kettering General Hospital, England report 7 tumours of the renal pelvis with positive urine cytology in 5 and 6 tumours of the ureter with positive urine cytology in 5. They consider that routine cytological examination of the urine offers the prospect of earlier diagnosis of transitional cell carcinoma of the renal pelvis and ureter than do other methods of investigation. They believe that a repeated finding of malignant cells in ureteric specimens collected from one side, with their absence in ureteric specimens from the opposite side indicate that a carcinoma is present even if it cannot be confirmed radiologically. There is an excellent presentation of the variety of cells seen in the urine in different conditions and these are compared with carcinoma cells. They describe 3 grades of cells depending on the degree of malignancy and invasion and consider this may be a guide to treatment. They discuss 3 patients with false negative results but apart from these the findings in the remainder led to an earlier diagnosis. They perform differential urine cytology as a routine investigation.

"Vesico-Colic Fistula due to Diverticulitis." MURRAY T. PHEILS. (1972, 41, 237-240.)—Professor Pheils from the Repatriation Hospital, Concord, New South Wales, presents 55 patients with vesico-colic fistula due to diverticulitis. The mean age was 64 years with an age range of 45 to 87. There were 41 males and 14 females. Pneumaturia is the most frequent symptom and the fistula can only be demonstrated by cystoscopy or barium enema in about one-third of patients. He confirms the experience of other authors that proximal defunctioning colostomy does not prevent recurrent infection and eventual death from renal failure and considers that resection of the fistula with the affected segment of bowel is the only cure. He classifies the disease into 3 groups and advocates a different type of resection for each. Group 1 occurs when a pericolic abscess ruptures into the bladder. The patients in this group rapidly become seriously ill and a transverse colostomy is established following antibiotic and supportive therapy. They are thus submitted to a 3-stage resection. Patients in Group 2 have a pericolic abscess or phlegmon firmly adherent to the bladder. He believes that these should be excised at a primary operation and a primary anastomosis achieved but protected by a temporary proximal colostomy. Group 3 is the most frequently presenting group with a small fistula between the colonic diverticulum and the bladder. He suggests that these patients should

be treated by a 1-stage primary resection and anastomosis. In all 3 groups the bladder is closed and catheter drainage continued postoperatively.

The British Journal of Radiology

By CHARLES NICHOLAS

"Xanthogranulomatous Pyelonephritis." J. C. GINGELL, J. ROYLANCE, E. R. DAVIES and J. B. PENRY. (1973, 46, 99-109.)—The authors describe the clinical and radiological findings in 11 cases investigated at the Department of Urology and Radiology, United Bristol and Southmead General Hospitals. In all cases the nephrectomy specimens exhibited bright yellow masses consisting of xanthoma cells in granulomatous tissue. The disease is unilateral and usually affects the whole kidney, the calyces and pelvis being dilated and eroded. There is extensive perinephric fibrosis. No absolute clinical diagnostic criteria exist. The disease can only be suspected. All patients had a history of chronic urinary tract infection (*E. coli*, *B. proteus*, *M. tuberculosis*), loin or supra-pubic, ill health, haematuria or palpable kidney, pyrexia, a raised ESR or leucocytosis. Renal outlines were not clear in plain X-rays and calculi were present in 2 cases. High dosage I.V.P. shows clubbing of calyces, inadequate filling and in some poor renal function or absent nephrogram. Retrograde pyelography demonstrated hydronephrosis in some and failed in 3. Selective renal arteriography in 3 showed avascular areas and sparse attenuated intrarenal arteries with pruning of distal branches. The opposite renal arterial trees were normal. Clinically xanthomatous pyelonephritis may resemble renal tuberculosis. Renal cell carcinoma can be excluded by arteriography. Treatment is by nephrectomy and the prognosis is good.

The British Journal of Surgery

By D. M. ESSENHIGH

"Embryonic Rhabdomyosarcoma of the Urogenital Tract." S. GHAZALI. (1973, 60, 124-128.)—Experience of 42 patients seen at Great Ormond Street between the years 1945-71 is analysed. These arose from various sites, 24 in the bladder, 9 in the prostate, 3 in the spermatic cord, 4 in the vagina and 2 in the broad ligament. The median age of presentation was 1 year 9 months in the bladder, 3 years 6 months in the prostate, and other tumours well scattered over the ages 6 months-13 years. The presentation of these tumours is described. The preferred treatment is surgical: radiotherapy and chemotherapy are unhelpful although utilised if there is doubt about the completeness of excision of the primary tumour. The results of treatment are bad, except in polypoid tumours of the bladder. The only survivors in this series are 11 with polypoid tumours of the bladder, 2 prostatic tumours (follow up 7 and 9 months only) 2 spermatic cord tumours (10 years later) and one broad ligament tumour (6 years later). It is believed that if there is no local recurrence of tumour within 2 years of surgery that the outlook is probably good.

"Further Progress with Reconstruction of the Extrophied Bladder." D. INNES WILLIAMS and JAMES E. KEETON. (1973, 60, 203-207.)—Two series of recon-

structions of the classic extrophied bladder are reported from Great Ormond Street. These cover the years 1949-63 (80 cases seen, reconstruction in 51) and 1963-69 (36 cases seen, reconstruction in 19). The basic methods of reconstruction are the same in both series and are briefly described. The major differences are in selection of patients—choosing those with the larger, more supple, healthy bladders; less effort to obtain a tight closure; and delayed closure—average 8-12 months in the first series, 16 months in the second. Acceptable continence was obtained in 9.8% of those reconstructed in the first series and in 31% of the second. There is also considerable improvement in morbidity in the second series, both a decrease in early surgical complications and a reduction in delayed urinary tract damage. The authors review the reasons for these differences. They believe that penile lengthening, valuable later to allow normal intercourse, has no effect on continence. Pelvic osteotomy is of doubtful value and is now used only if the gap between the pubes is very wide. Assessment of loose closure of the bladder neck is uncertain, the best results are found when muscle tissue in this region is well formed. Bladder enlargement with intestinal patches has not improved the results. Reflux-preventing operations have diminished late urinary tract damage. The authors believe that with careful selection about 50% of cases are suitable for reconstruction. Their policy for the future will be first, to lengthen the penis early on, second, to delay closure to the second or third year life and, thirdly, to avoid pelvic osteotomy whenever possible.

"The Coagulum Pyelolithotomy." V. J. PATCH. (1973, 60, 230-236.)—This report from Offenbach, West Germany, describes the technique of installing a coagulable fluid into the pelvicalyceal system in order to trap small stones and allow their easy removal. Solutions used are 1 g fibrinogen in 25 ml Ringer's solution and 100 units of thrombin in 3 ml of isotonic saline. These are kept separately in a water-bath at 37°C until needed. A funnel-shaped catheter is inserted into a small pyelotomy incision, and the capacity of the pelvi-calceal system is measured. The 2 solutions are mixed and quickly injected through the catheter, slightly overdistending the pelvis. Coagulation takes 30 seconds. After 7 minutes the catheter is withdrawn, the pelvic incision enlarged, and the cast is gently teased out of the kidney. The author has used this method in 22 patients, and gives details of 2 cases. There were 5 early technical failures; in the remainder, all stones were removed. Evidence is quoted to show that coagulum left behind in the kidney dissolves within 72 hours and is harmless. This is claimed to be a safe and atraumatic method of recovering stones from the kidney.

Deutsche Medizinische Wochenschrift

By JOHN GRIEVE

"Early Treatment of Testicular Maldescent." W. C. HECKER, H. A. HEINZ and W. MENGEL. (1972, 97, 1325-1329.)—In a series of 471 biopsies from maldescended testes these authors from Krefeld found severe reduction or complete loss of spermatogonia after the second year of life. During the first 2 years the spermatogonia count has reached the lower limit

of normal. The tubular diameter of the undescended testis remains much less than normal. These findings are in unilateral maldescent and in the contralateral testis 40% were normal, 47% showed a reduction in spermatogonia and 12.5% an absence of spermatogonia. The authors believe that something in relation to the maldescended testis causes these changes and advocate orchidectomy to remove this malign influence if the testis cannot be retained in the scrotum.

"Infra-red Spectroscopy of Urinary Calculi." A. HESSE, H. J. SCHNEIDER and E. HIENZSCH. (1972, 97, 1694-1701.)—Infra-red spectroscopic analysis complements X-ray crystallography and thermoanalysis as a quick and informative method for determining the composition of urinary calculi. Among 2,000 stones the main components were uric acid (16.2%), uric acid dihydrate (2.5%), cystine (0.5%), protein (1.7%), whewellite (48.5%), weddellite (17.5%), struvite (8.8%), carbonate apatite (2.2%), brushite (0.2%) and other (1.2%). Identification was achieved by comparison with spectra of pure substances and known mixtures.

La Nouvelle Presse Médicale

By JOHN GRIEVE

"Cancer of the Kidney with an Unvisualised Kidney on Intravenous Pyelography." V. BISMUTH, B. VELLON, J. P. FENDLER, M. BLERY and J. C. GAUX. (1972, 1, 2373-2378.)—No excretion by the affected kidney was seen in 3 patients with renal carcinoma. The authors from Paris stress that this is insufficiently appreciated and occurs in 10%-25% of renal carcinoma patients. There are different explanations for failure of visualisation but renal vein and caval thrombosis are less common than has been suggested. Renal arteriography can be of great help in the "silent" kidney.

Surgery

By R. T. BURKITT

"Extragenadal Germ Cell Tumors." DOUGLAS E. JOHNSON, JOHN P. LANERI, CLIFTON F. MOUNTAIN and MARIO LUNA. (1973, 73, 85-90.)—The authors describe 19 cases of extragenadal germ cell tumours which have occurred at the Houston Medical Center during the 27 years 1944-71. These tumours were found as follows—8 in the retroperitoneal space, 7 in the anterior mediastinum, 2 in the pineal body, 1 in the presacral space and in 1 case owing to the number of metastases the origin could not be determined. Of these tumours 8 were seminomas, 5 teratomas, 4 choriocarcinomas and 2 mixed tumours. In all cases the malignancy was extremely high and only 2 patients survived 3 years. The type of tumour bore no relationship to its site of origin.

Surgery, Gynecology and Obstetrics

By THOMAS MOORE

"Simultaneous Bilateral Nephrectomy from a Posterior Approach." JAGDISH PATIL, ALAN H. BENNETT,

GEORGE L. BAILEY, EDWARD M. MAHONEY and J. HARTWELL HARRISON. (1972, 134, 764-766.)—Since 1956 when the first bilateral nephrectomy was carried out at the Peter Bent Brigham Hospital, more than 200 patients have been operated upon. An analysis of 100 cases, in which the simultaneous bilateral approach by 2 surgical teams through the beds of the 12th ribs was used, has shown that, in spite of the poor state of such patients, there was no mortality and minimal morbidity. This approach is not used in cases of bilateral polycystic kidneys.

"Stress Ulcers in Post-traumatic Renal Insufficiency in Patients from Vietnam." RONALD P. FISCHER and JOHN F. STREMPLE. (1972, 134, 790-794.)—The authors from the Walter Reed Army Institute of Research, Washington, Columbia, report on 96 patients with post-traumatic acute renal insufficiency treated by the U.S. Army's dialysis unit in Vietnam. 19 developed stress ulcers. Of these, 16 suffered from gross bleeding from the upper gastrointestinal tract. In 8 cases of massive haemorrhage from the stomach, surgery was undertaken. 18 of the 19 cases suffered from septicaemia which was caused by a gram-negative organism in 13 of the 14 so investigated. 18 patients died. In 12, sepsis was the main cause.

"Persistent Experimental Hypertension and Progressive Bilateral Renal Artery Occlusion." JAMES C. STANLEY, CALVIN B. ERNST, GARY L. HOFFMAN, BARRY F. BATES and WILLIAM J. FRY. (1972, 134, 981-984.)—The authors, from the University of Michigan Medical Center, Ann Arbor, have caused progressive bilateral renal artery occlusion using casein resin constrictors, which has proved an effective means of producing experimental hypertension.

"Renal Artery Catheterization using Silicone Tubing." JOHN J. MCDEVITT IV and JOHN J. MURPHY. (1972, 135, 99-100.)—The authors, working in the Department of Surgery, University of Pennsylvania School of Medicine in Philadelphia, have modified a simple technique for experimental catheterization of arteries, using silicone in place of polyvinyl chloride tubing.

"Histocompatibility and the Success of Intra-familial Renal Transplantation." JEREMIAH G. TURCOTTE, RICHARD F. HAINES and NICHOLAS J. FEDUSKA. (1972, 135, 193-198.)—The authors, working in the Surgical Division of the University of Michigan Medical Center, Ann Arbor, present a very detailed analysis of the results of 55 consanguineous renal transplants. In all lymphocyte antigens of donors and recipients had been determined by the microdroplet technique described by Mittal. The results were always better with matching grafts. Grafts with 1 antigenic group mismatch were more satisfactory than those with more than one; this was true for both sibling and parent/child graft. The greater the incompatibility, the more numerous the complications. Transplant function and amount of prednisone required were not related to the antigen match.

"The Significance of Antivascular Endothelium Antibody in Renal Transplantation." JAMES CERILLI, JOHN E. JOSEPH and ARLENE C. MILLER. (1972, 135, 246-252.)—The authors report their investigations carried out in the Department of Surgery in the

College of Medicine, Ohio State University, Columbus, on serum samples obtained from persons who were either normal, pre-sensitised, exposed to mechanism of pre-sensitisation or recipients of renal allografts by the indirect fluorescent antibody technique against arterial tissue from either kidney allograft recipients or donors. They have shown the test to be both sensitive and reproducible and as effective as a lymphocytotoxicity test in detecting pre-sensitisation. They present detailed evidence suggesting that the direct fluorescent antibody technique may be superior to other *in vitro* methods of detecting pre-sensitisation and therefore useful in prognosis.

"Operative Treatment, Surgical Approach and Related Complications in 195 operations upon the Adrenal Glands." MOGENS Blichert-Toft, ANNETTE BAGERSKOV, KNUD LOCKWOOD and EIVEN HASNER. (1972, 135, 261-266.)—From the records of the Department of Endocrine Surgery, University Clinic, Copenhagen, the authors report results of 195 operations upon adrenal glands, from 1945 to May 1971. 82% of patients had adrenal disease, the remainder either had a suspicion of such disease or the operation was part of the treatment of metastatic carcinoma of the breast. Only 20% had complications; the commonest one of which was thrombophlebitis, particularly in patients with Cushing's disease. Both trans-abdominal and lumbar approaches were used. From their analysis the authors strongly recommend the former.

"Vascular access for Patients on Maintenance Dialysis." R. L. LAWTON and L. S. SHARZER. (1972, 135, 279-283.)—In patients on maintenance dialysis, adequate sites for cannulation eventually becomes a problem and the authors detail some of the methods which can be used to extend the sites available. Although such techniques appear as a minor surgical exercise, many patients' long-term survival will depend upon them.

"Renography in the Evaluation of Patients with Ileal Conduits." MARK S. SOLOWAY, GEORGE H. MYERS, GERALD JOHNSTON and ALFRED S. KETCHAM. (1972, 135, 521-524.)—These workers have studied renal function in 30 patients with ileal conduit urinary diversions by intravenous urography and renography. They have shown that when the latter is carried out with the patient in the sitting position the results are in most cases very comparable and they suggest that renography is a sufficient and accurate method of follow-up.

"Renal Preservation by Hypothermic Storage plus Pulsatile Perfusion." W. A. STERLING, J. C. PIERCE, H. M. LEE, D. M. HUME, N. E. HUTCHER and G. MENDEZ-PICON. (1972, 135, 589-592.)—At the well known centre in Richmond, Virginia, the authors have developed a method of storing cadaveric kidneys by simple hypothermia, followed by pulsatile perfusion. They detail adverse factors affecting the kidneys but have shown the feasibility of sharing cadaveric kidneys between widely separated institutions.

"The Embryology of High Anorectal and Associated Genitourinary Anomalies in the Female." ROBERT J. JOHNSON, MORTON PALKEN, WALTER DERRICK and ALEXANDER H. BILL. (1972, 135, 759-762.)—The authors consider in detail the basic development of

the rectum, the lower genital and urinary tracts in the female. From a clinical experience of 10 cases they correlate the abnormalities with the embryology and, as far as possible, explain them.

"Validity of the Intravenous Pyelogram in Assessment of Renal Function." R. MARK WILKEMEYER and WILLIAM H. BOYCE. (1972, 135, 897-900.)—The authors have compared renal function as estimated by the density of the calyceal and pelvic shadows in intravenous urography with detailed differential renal function tests in 4 hypertensive stone forming patients. The results confirmed, as was expected, that intravenous urography is not an accurate method of assessing renal function.

"Ruptured Abdominal Aortic Aneurysms in the Presence of Horseshoe Kidneys." C. GENE CAYTEN, ARNOLD V. DAVIS, HENRY D. BERKOWITZ, BROOKE ROBERTS. (1972, 135, 945-949.)—In a review of the literature, the authors, who work in the University of Pennsylvania Hospital, found 23 patients with horseshoe kidneys who had been operated upon for abdominal aortic aneurysm; in only 1 had rupture occurred. They report 2 additional patients with a ruptured aortic aneurysm and 1 without; the latter, and 1 of the former, survived. The congenital anomaly makes operation more difficult; they stress it is important to have careful angiographic study of the vascular supply to the kidney previous to operation. Division of the isthmus, if necessary, can then be carried out more safely during replacement of the aneurysm.

"Ureteral Replacements." AUGUST P. HOVNANIAN. (1972, 135, 801-810.)—The author, a member of the staff of the Chicago Medical School, presents a collective review of the literature up to September 1971 on ureteral replacements, under the following headings: (1) Indications for replacement of the ureter. (2) Criteria for choice of procedures. (3) Non-biological substitutes. (4) Biological substitutes. The latter include bladder flap operations, ileal replacements and bladder mucosal replacements.

"Experience with Hyperparathyroidism." A. J. STUBBS and R. T. MYERS. (1973, 136, 65-67.)—Of 150 cases explored in the North Carolina Baptist Hospital for hyperparathyroidism, 16 had no demonstrable abnormality. Of the remaining 134 cases, 110 suffered from adenomata, 17 primary hyperplasia, 3 secondary hyperparathyroidism, 1 carcinoma, 1 carcinoma and adenoma and in 2, the histologist could not make a definite decision as to whether the appearances were due to carcinoma or adenoma. 83 were female and 51 male. In 95 patients renal calculi were present or had been present, 7 patients suffered from nephrocalcinosis, 7 patients suffered from demonstrable peptic ulcer, 4 patients suffered from pancreatitis with a raised serum amylase and 1 had pancreatic calcification. Six patients had a hypercalcaemia of more than 15 mg per 100 ml and marked general signs and symptoms. The authors regard 11 mg per 100 ml as the level of serum calcium which suggests hyperparathyroidism; similarly a serum phosphorus below 3 mg per 100 ml is suggestive of the disease. They reiterate the general experience that, in spite of all modern techniques, the diagnosis is still not always certain and suggest that some bio-immunoassay may be the answer.

"The Objective study of Incontinence after Repair Operations." C. P. BATES, H. LOOSE and S. L. R. STANTON. (1973, 136, 17-22.)—From the Middlesex Hospital the authors report their investigations of 75 patients who had been treated unsuccessfully for incontinence of urine by repair operations. Using a method of simultaneous cinepressure flow cystography, they have shown that many, without any demonstrable evidence of a neurological lesion, develop uninhibited detrusor contractions on standing or coughing. They regard this as the primary cause of the leakage, not sphincter mechanisms as is usually believed and discuss the significance of such objective findings in relation to rational treatment.

"Evaluation of Simple Methods for assessing Renal Ischaemia Injury." I. R. HARDIE, G. J. A. CLUNIE and G. M. COLLINS. (1973, 136, 43-46.)—Working in the Department of Surgery of the University of Queensland, Brisbane, the authors have studied 4 tests, the measurement of oxygen consumption, reduction time of tetrazolium salt by cortical tissue, the leakage of intracellular enzymes into a perfusate and surface electrometry, as a measure of the degree of renal ischaemia in dogs and rabbit kidneys. They have shown that renal cortical oxygen consumption and the initial washout of lacto-dehydrogenase by renal perfusion were closely related to the duration of renal ischaemia. They suggest the latter to be the most suitable for use in human cadaveric renal transplantation.

Der Urologe

By JOHN GRIEVE

"The Pathological Anatomy of Disturbances of Male Fertility." C. HEDINGER. (1972, 11, 201-204.)—The author from Zurich reviews the testicular changes in 373 patients investigated for infertility. In extra-testicular disease he commonly found occlusion of the vas. Where the testis was involved primary hypogonadism was of greater importance than secondary hypogonadism. Chromosomal aberrations are stated to be responsible for testicular mal-location and malformation with consequent infertility. A normally sited healthy testicle may be damaged and give rise to infertility.

"Prophylaxis and Conservative Treatment of Male Infertility." B. VON RUTTE. (1972, 11, 205-209.)—In only about 10% of cases of male infertility the author believes that treatment may help. The reason for this is the limited knowledge of the physiology and pathology of spermatogenesis. He has used vitamins A and E alone and in combination with androgens and where indicated gonadotrophins clomiphene, tri-iodo-thyronine and arginine. With these regimes he has succeeded in restoring the ejaculate to a more normal appearance.

"Distal Urethral Stenosis in Women." N. O'DONOGHUE and H. LIPSKY. (1972, 11, 252-257.)—In 30 women, with recurrent voiding difficulties, urological gynaecological and radiological investigations were done. Measurements of urine flow rate were also done and repeated after 1 week in 17 of the patients. Voiding pressure recordings were made

simultaneously and by studying the results the authors concluded that 20 patients had distal urethral stenosis. (Judging from the calibration of the urethra shown in Table 2 the stenosis was not severe in many of the patients.) The authors believe that dilatation is the best form of treatment and this would accord with the experience of others.

Venezuelan Journal of Urology

By CLIVE CHARLTON

"Prostatic Biopsy by Rectal and Perineal Puncture." OSCAR CHACON. (1971, 23, 211-219.)—Using the Vim-Silverman-Franklyn needle, the author biopsied 40 glands by each route. Local anaesthetic was used in the perineal approach and the average time taken for the whole procedure was 7 minutes. When biopsying the glands through the rectum no anaesthetic was used and the time taken was 2 minutes. Employing the perineal route, inadequate biopsies were obtained in 6 cases; and with the rectal route this deficiency occurred only 3 times. In 41 cases prostatectomy was undertaken and there were no discrepancies in the histology when comparing biopsy and operative specimens. Hospitalisation is not considered essential. Complications of the procedures (including pain) were equally uncommon in both groups.

Zeitschrift für Urologie

By JOHN GRIEVE

"Protein Stones in the Urinary Tract. Methods for their Analysis." G. HORN and A. HESSE. (1972, 65, 801-813.)—A series of 16 protein stones in the urinary tract has been collected. Eight of these disappeared spontaneously, and 8 occurred along with other stone like structures. The stones were analysed by X-ray diffraction and infra-red spectroscopy, and when soft histological investigation was done. Protein stones are rather more common than has hitherto been believed.

"The Staining of Uric Acid Crystals with Methylene Blue." J. KLEEBORG. (1972, 65, 619-629.)—In this work from Haifa the author treated uric acid crystals from urine and bladder stones with an aqueous solution of methylene blue. When the stone was fully formed staining by methylene blue was minimal but in the developing stone definite staining occurred. The strength of colour developed was more related to the duration of the staining than the strength of the solution used. The author believes that this technique may have a role in the study of stone formation in bladder and kidney.

be drawn in Indian ink. Lettering *must* be indicated on a transparent cover. Legends to figures should be typewritten on a separate sheet of the manuscript. Tables, unless they are very small, should also be typewritten on separate sheets. The position of illustrations and tables should be indicated in the margin of the text.

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Brief reports (preferably with 1 and not more than 2 illustrations) of unusual cases not published elsewhere may be submitted as summaries of not more than 200 words for consideration for publication as Short Case Reports. They should comprise (1) a Title, (2) Case description and (3) a brief Comment. The authors and references are each limited to 3. The titles of these reports will usually be recorded in *Index Medicus* and by MEDLARS.

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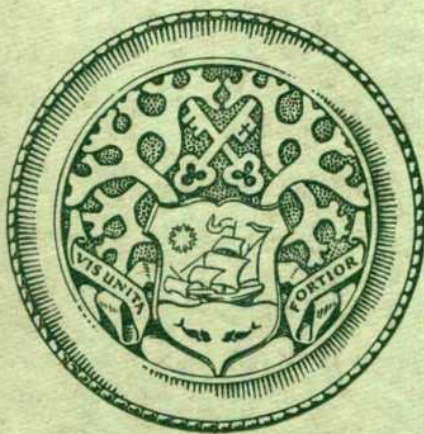
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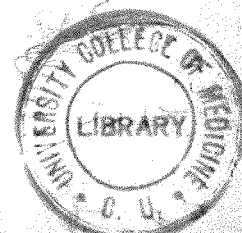
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- 1 Leading Article, *Brit med J*, (1969), **1**, 525.
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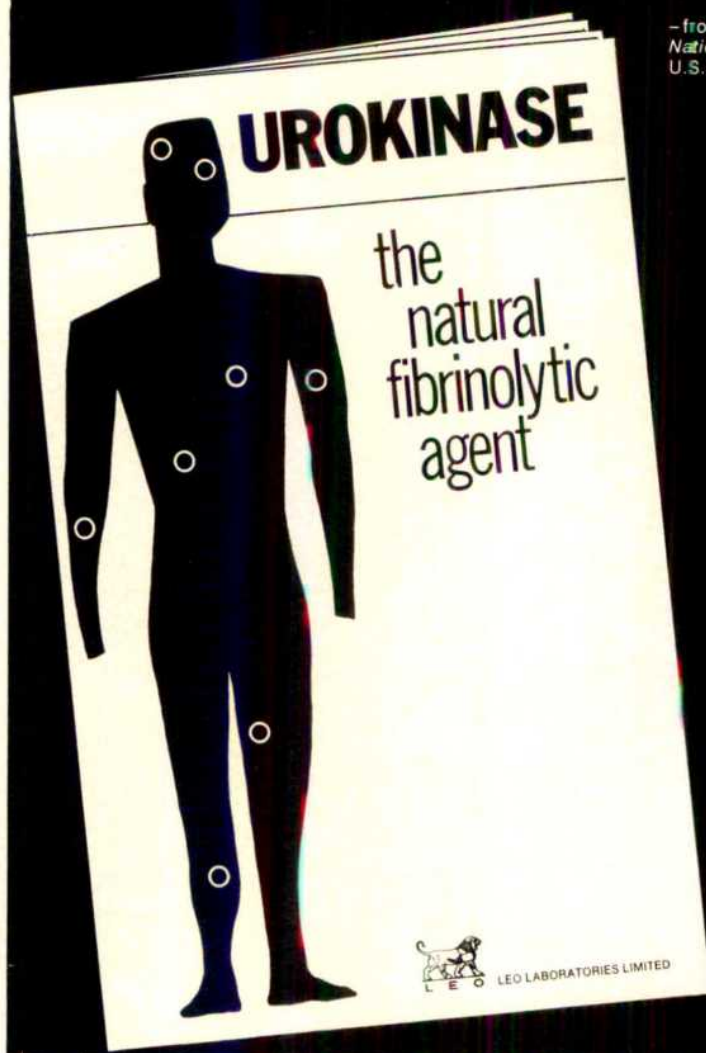
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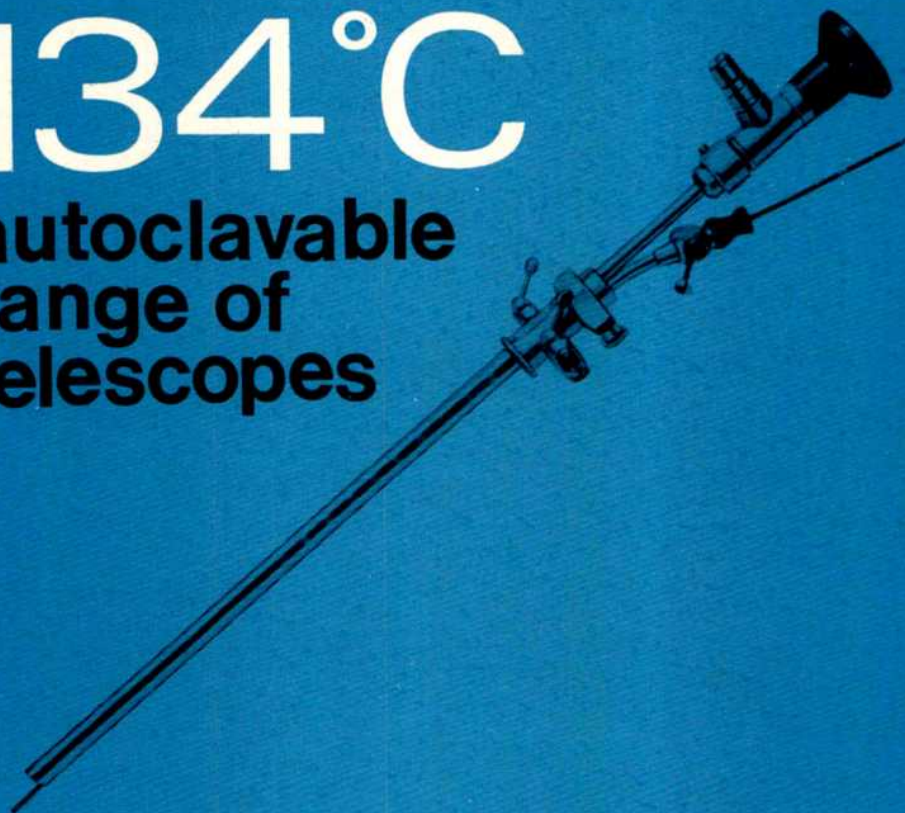


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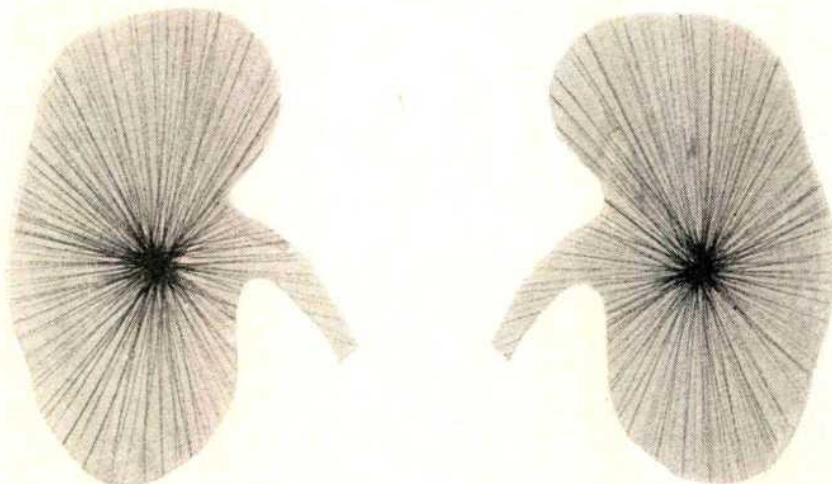
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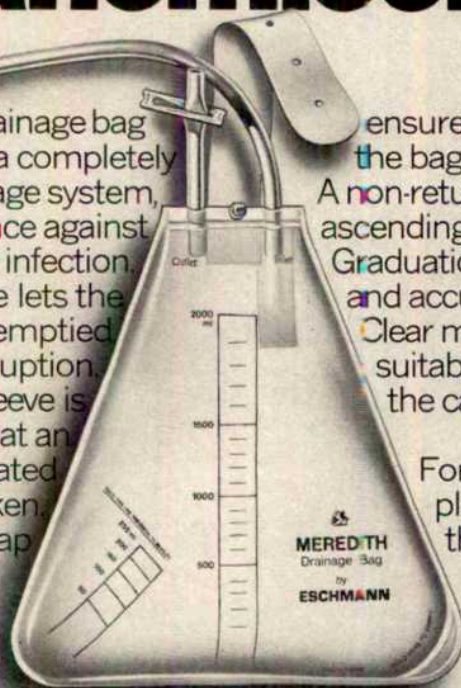


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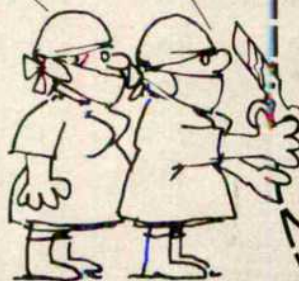
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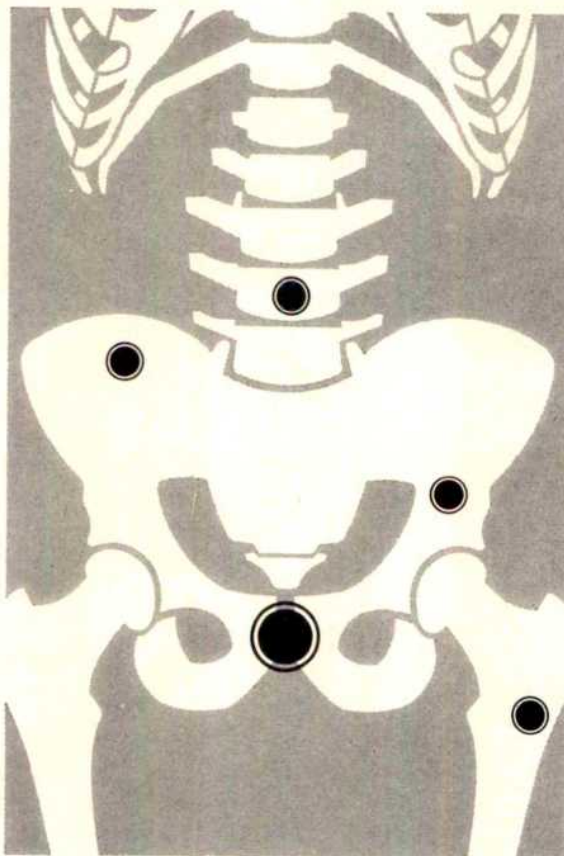
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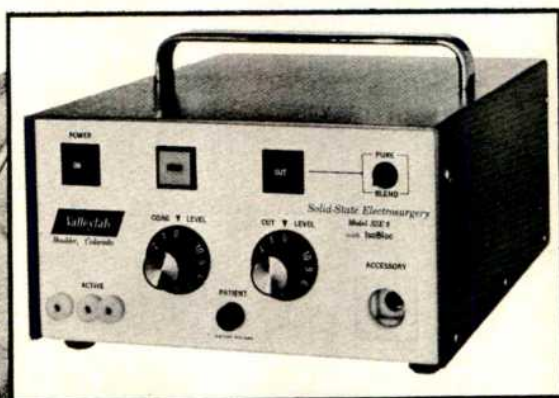
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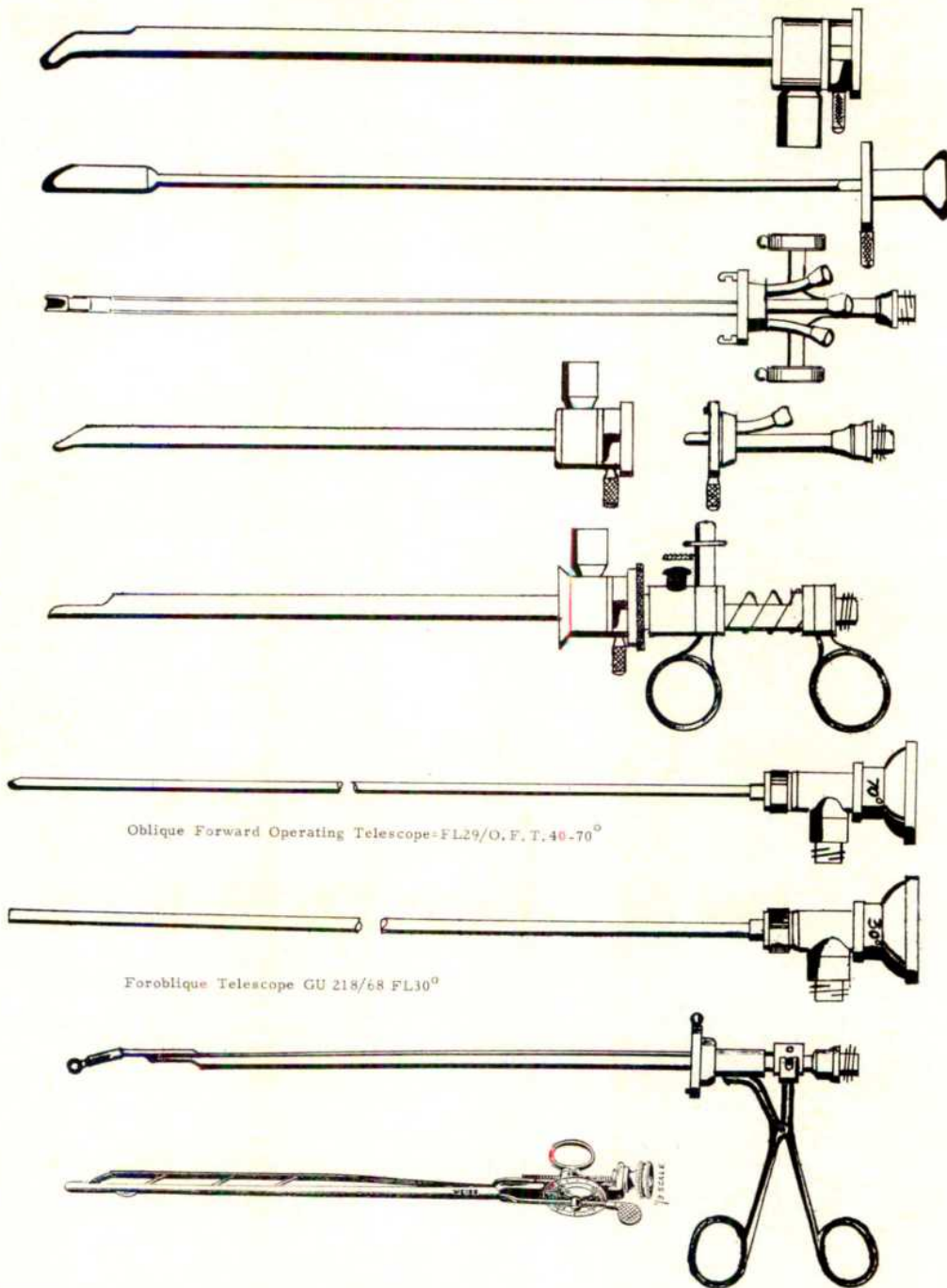


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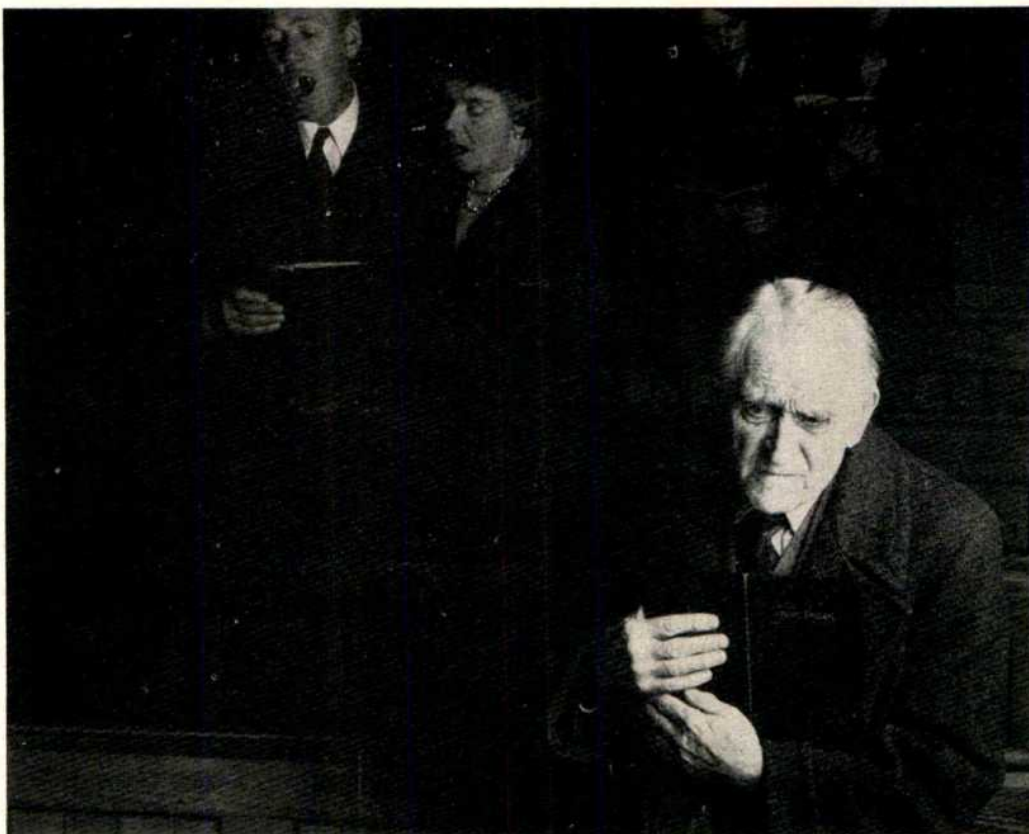
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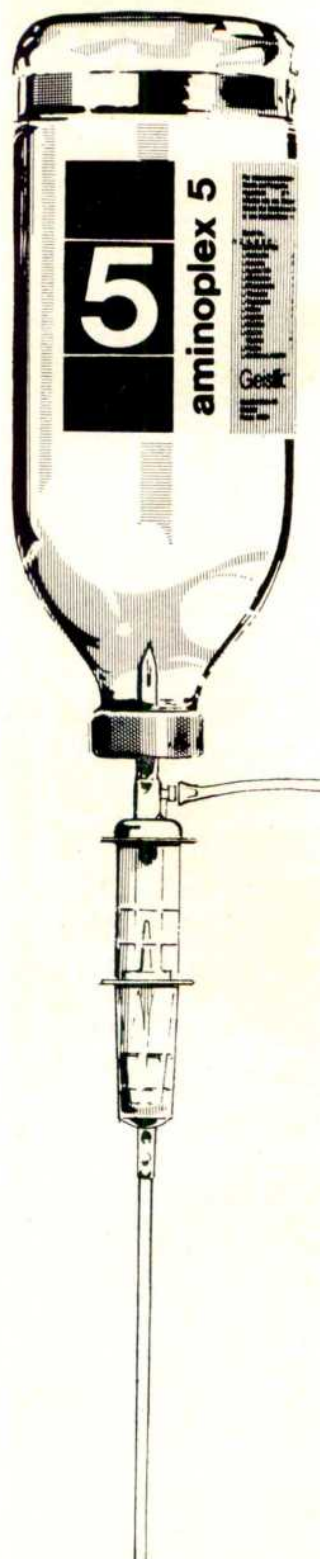
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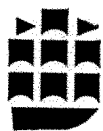
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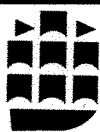
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The Long-term Follow-up of Anderson-Hynes Pyeloplasty for Hydronephrosis

R. G. NOTLEY and J. M. BEAUGIE

The London Hospital, London E1 2AD

Faced with an obstructed retrocaval ureter Anderson and Hynes (1949) devised a method to meet the problem which has since in this country become the standard operation for hydronephrosis due to obstruction at the pelvi-ureteric junction. It is thought (Notley, 1971) that excessive fibrosis in the muscular and submucosal layer of this segment of the ureter prevents it from dilating to accommodate the increased flow of urine during diuresis, so that the excision of the fibrosed pelvi-ureteric segment in the Anderson-Hynes pyeloplasty ought to make it a rational treatment for this type of hydronephrosis. In the event the immediate results are good in clinical terms; most patients are relieved of their symptoms at once. True, the postoperative pyelogram rarely returns to normal (Anderson, 1962; Sunderland, 1963) nor does the renal function improve as assessed by isotope renography (Davies, Jones and Croft, 1969). Nevertheless the short-term results are generally agreed to be excellent. What is still far from clear, however, is the long-term prognosis, for we have no data as to whether good early clinical results are maintained in the long-term, or whether progression of the underlying fibrosing condition has been halted, since published series have covered a relatively short period after operation. It was to try and answer some of these questions that we set out to evaluate the results of Anderson-Hynes pyeloplasties which were performed 5 to 15 years ago.

Table I

33	Patients	24	Male
		9	Female
37	Pyeloplasties	16	Right-sided
	(Bilateral in 4 cases)	21	Left-sided

In the records of the St Peter's Group of Hospitals and the London Hospital there were 54 patients treated by Anderson-Hynes pyeloplasty between the years 1956 and 1966. Five of them had subsequently required nephrectomy. Of the remaining 49, 33 were traced—24 men and 9 women—among whom 4 had undergone bilateral operations, so that we could follow the fate of 37 pyeloplasties (Table I). All of the 33 patients attended hospital for interview, clinical examination and intravenous pyelogram. The urine was cultured and the blood urea measured.

Results

Symptoms. All 33 patients were without any symptoms, none had any clinical manifestation of urinary tract disorder and all had a normal blood urea. One patient was at first found to have

infected urine at the time of examination, but this was not confirmed in subsequent specimens of urine. On comparing their symptoms now with those present before operation the most striking improvement has been in relief of pain, for most patients complained of loin pain before operation (Table II).

Table II

Symptoms	At Presentation	At Follow-up
Loin pain	30	0
Infection	6	1
Haematuria	6	0
Stone	5	0
Calculous anuria	1	0



Fig. 1. A, Preoperative intravenous pyelogram (patient P.K.).



Fig. 1. B, Intravenous pyelogram 10 years after bilateral Anderson-Hynes pyeloplasty.

Urograms. Our original intention had been to measure the area of the renal parenchyma by planimetry of the nephrographic shadow in pre- and postoperative films in order to see whether further loss of renal substance had occurred since the pyeloplasty, but there were only 1 or 2 cases in which the renal outline could be made out on the original films, most of which were more than 10 years old. By contrast, so much have radiological techniques improved in the decade of this review that the renal outline could be easily seen in all the more recent films. Nevertheless, in spite of being unable to quantify our impressions certain features were very obvious. First, all 37 kidneys showed considerable hydronephrosis with calyceal clubbing on the preoperative films, but in all cases sufficient concentration of the dye to delineate the renal pelvis, albeit not until the 1- or 2-hour films. In the follow-up pyelograms the renal pelvis and calyces could always be seen on the 5-minute film and all drained satisfactorily. Usually the size of the renal pelvis was much reduced by comparison with the preoperative pyelograms, but in no case did the shape return completely to normal and in many instances the calyces retained their "clubbed" outline. None of these kidneys had a worse pyelogram 5 to 10 years later than the films taken soon after operation. It was clear that further deterioration had not occurred over the intervening years.

Examples

1. P. K. male, 24 years old, presented with bilateral loin pain and episodes of urinary infection without haematuria. The preoperative pyelogram (Fig. 1, A) showed bilateral hydronephrosis. An Anderson-Hynes pyeloplasty was performed on the right side and 2 months later a similar operation was done on the left. The patient was relieved of his symptoms immediately and has remained well ever since. Ten years later his pyelogram (Fig. 1, B) shows rapid appearance of the dye in both kidneys, which drained well. The pelvi-calyceal outline remains distorted.



Fig. 2. A. Preoperative intravenous pyelogram (patient D. P.).



Fig. 2. B. Intravenous pyelogram 12 years after right Anderson-Hynes pyeloplasty.

2. D. P., female, aged 27 years, complained originally of right loin pain, but had no urinary symptoms. The pyelogram (Fig. 2, A) showed a right hydronephrosis. Her symptoms were permanently relieved by pyeloplasty. After 12 years the pyelogram showed residual pelvic dilatation, but early appearance of the contrast medium and good drainage (Fig. 2, B).

Comment

This study shows that the good early results of the Anderson-Hynes pyeloplasty for hydronephrosis are maintained over periods from 5 to 15 years. All the patients studied were symptomless at the time of review. It is unlikely that renal denervation is responsible for the permanent relief of pain over such a period since if autonomic nerves are divided distal to their ganglia they will regenerate in a matter of weeks or months; it is more likely that removal of the obstruction is the responsible factor.

It is less easy to say with certainty that the progressive nature of the underlying condition in the ureter or renal parenchyma has been halted by the operation in the absence of a means of measuring renal mass or function, but the appearances of the pyelograms suggest that no further deterioration has occurred and that certainly all the kidneys continued to drain well.

Physical deformity of the renal pelvis and calyces persists in almost all cases, but this is hardly surprising since the long-term effects of ureteric obstruction upon the pelvis and the calyces are muscular hypertrophy proceeding to fibrous replacement of the muscle fibres—an irreversible situation—and once the renal parenchyma and papillae have undergone atrophy there is no reason why they should regenerate. Clubbing of the calyces caused by loss of papillae will necessarily be a permanent feature as will pressure atrophy of the renal cortex. It follows from this that if one is to save renal parenchyma from permanent destruction it is necessary to operate as soon

as possible in the natural history of hydronephrosis. Perhaps in future early diagnosis may be made with certainty by using pressure measuring techniques and by the techniques of screening after giving a high dose of contrast medium together with a diuretic. What does emerge from this follow-up is that early postoperative success is likely to be maintained and in this regard the operation of Anderson and Hynes is again vindicated.

We are most grateful to the surgeons of the St Peter's Hospitals and those of the Department of Urology of the London Hospital for their permission to study their patients.

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How Accurate is Diagnostic Ultrasound in Renal Disease?

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The usefulness of ultrasound in the investigation of renal lesions is now well established (Damascelli *et al.*, 1968; Barnett and Morley, 1971; Holm, 1971; Kyle *et al.*, 1971; Mountford *et al.*, 1971; Barnett and Morley, 1972a; Holm, Rasmussen and Kristensen, 1972).

Its main benefit is distinguishing renal cysts from tumours and accuracy rates for this have varied from 71% to 96% (Barnett and Morley, 1972a).

During the last 18 months we have routinely used ultrasound in the investigation of a variety of renal diseases and we now wish to discuss our accuracy rates and analyse those cases in whom the procedure has been unhelpful or misleading.

Method

The apparatus used was an Austrian Kretz Technik unit. Either a 2 MHz or 5 MHz probe was employed in all patients. Longitudinal and transverse scans were made of both kidneys with the patient in the prone position. Occasionally with large masses scans were also made with the patient supine.

Difficulty was sometimes experienced with masses at the upper pole of the left kidney where the twelfth rib intervened between the probe and the mass, making it difficult to be certain whether or not the area was echo-free. In these circumstances it was found helpful to repeat the scan with the patient maintaining full inspiration. Part of the spleen may extend over the left kidney also making it difficult to obtain a satisfactory record of the upper renal pole (Holm *et al.*, 1972). This can lead to difficulty in differentiating a renal from an adrenal tumour.

The suppression control on the machine was turned well down or completely off during scanning to avoid suppressing small tumour echoes. Only if no echoes at all were received from within the mass, as seen on the A and B scans, was it considered to be a simple cyst (Fig. 1).

Renal cyst puncture was carried out under local anaesthesia using image intensifier control, after the pelvi-calyceal system had been outlined by an intravenous injection of contrast medium. Following puncture of the mass some fluid was aspirated for cytological examination for malignant cells and then an appropriate quantity of contrast medium was injected. Films of the mass outlined by contrast were taken and finally the fluid was aspirated.

Patients and Aims

66 studies were performed on 65 patients with ages ranging from 18 to 84 years with a mean age of 58 years. 22 were female and 43 male.

The sonogram was done to help answer one or more of the following questions:

1. An I.V.P. shows a space-occupying lesion in a functioning kidney—is it fluid-filled or solid?
2. An I.V.P. shows a non-excreting mass—is it fluid-filled or solid?

3. No function or evidence of a mass is seen on one side on an I.V.P.—is there a kidney present and, if so, is there a clue to its abnormality?
4. An I.V.P. shows a poorly excreting hydronephrosis—does the sonogram agree that this is wholly a fluid-filled mass?
5. An I.V.P. shows a normal kidney but there are symptoms seemingly referable to the kidney—can the sonogram add any information?

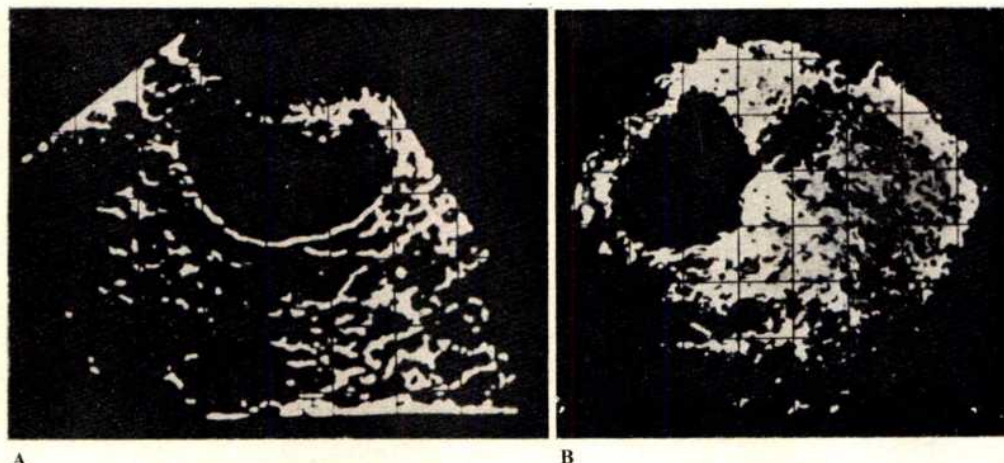


Fig. 1. Renal Cyst (G. C.). A, Longitudinal and B, transverse. These scans show a large transonic mass in the area of the left kidney. No echoes arise from within it and the wall is clearly defined.

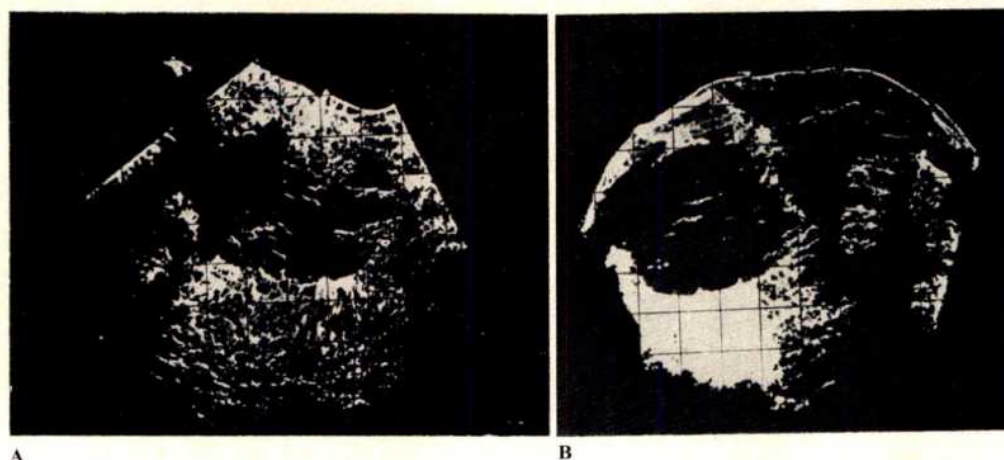


Fig. 2. Multicystic Disease (B. B.). A, Longitudinal and B, transverse. These scans show a grossly enlarged kidney, mainly transonic with many apparent septa within it. This was correctly interpreted as multicystic disease.

Results

Patients in whom the sonogram gave a positive and correct diagnosis

In 31 patients with a space-occupying lesion on an excretion urogram a confident diagnosis of simple cyst was made. This was confirmed by cyst puncture in all but 2 and these 2 patients had renal angiograms which showed the typical appearances of a cyst.

One patient's sonogram was interpreted as probably representing multiple cysts and this diagnosis proved later to be correct when the kidney was removed (Fig. 2).

A further 4 patients had sonograms diagnostic of cysts but were too infirm or otherwise seriously ill for confirmation by puncture or angiogram. Two patients had a poorly excreting hydronephrosis on an excretory urogram and sonar confirmed a large transonic mass consistent with this diagnosis.

Five patients had an excretion urogram showing a space-occupying lesion and a sonogram showing tumour; these were all confirmed at exploration (Fig. 3).

There was a group of 8 patients with no excretion on urography. Four were transonic masses and proved to be hydronephroses; the obstruction was caused by carcinomatous infiltration of the lower third of the ureter in 3 and a pelvi-ureteric junction obstruction in 1. The remaining 4 patients had sonograms indicative of tumours and these were later confirmed.

A group of 6 patients presenting with haematuria and/or pain have had normal urograms. The sonogram failed to show any abnormality and demonstrated a normal kidney in each case.

Finally 1 patient had no excretion on a urogram and no renal shadow. The sonogram failed to show a kidney and cystoscopy showed no ureteric orifice on this side. We feel that the sonogram confirmed an absent kidney.

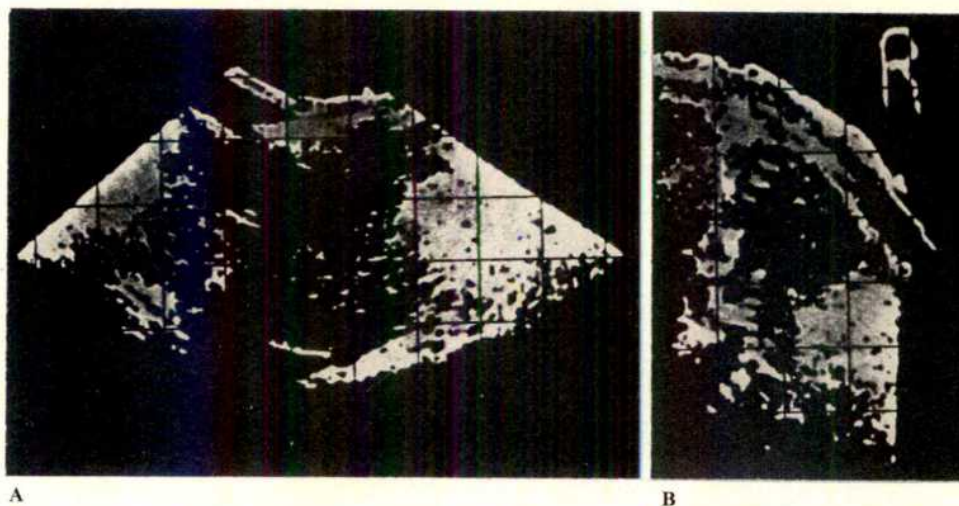


Fig. 3. Renal Carcinoma (R. S.). A, Longitudinal and B, transverse. These scans demonstrate a large renal tumour. The kidney is enlarged with no clear-cut outline. Multiple irregular tumour echoes are present.

Patients in whom the sonogram was misleading or failed to show the pathological process

The most serious diagnostic error was in a 31-year-old nursing sister who presented with right loin pain and a urogram which showed no excretion from the right kidney. A retrograde pyelogram confirmed a mass displacing the middle and lower calyces. The sonogram suggested a cystic lesion but, because the mass felt hard, an arteriogram was performed and this showed a highly vascular tumour which was subsequently removed. The kidney was, in fact, partially cystic but despite this, this investigation must be considered an error in ultrasound diagnosis.

A second patient presented with haematuria and an excretion urogram clearly showed a large renal pelvic tumour. This was not detected on the sonogram.

A third patient, a boy of 18 years, had spina bifida and an ileal loop diversion of urine. One kidney failed to excrete and a sonogram suggested a hydronephrosis on this side. This was clearly wrong, as when the kidney was removed shortly afterwards it was small, scarred and contracted.

The fourth patient in this group illustrated a more understandable error. A 65-year-old man was found to have a renal mass and the urogram showed a space-occupying lesion in an excreting

kidney. Sonar appearances suggested a tumour and on this basis the kidney was removed (Fig. 4). At the time of operation the kidney was thought to be replaced by a tumour but subsequently it was shown to be a multi-cystic kidney.

The fifth case was a lady who presented with right loin pain, a soft tissue mass and a calculus

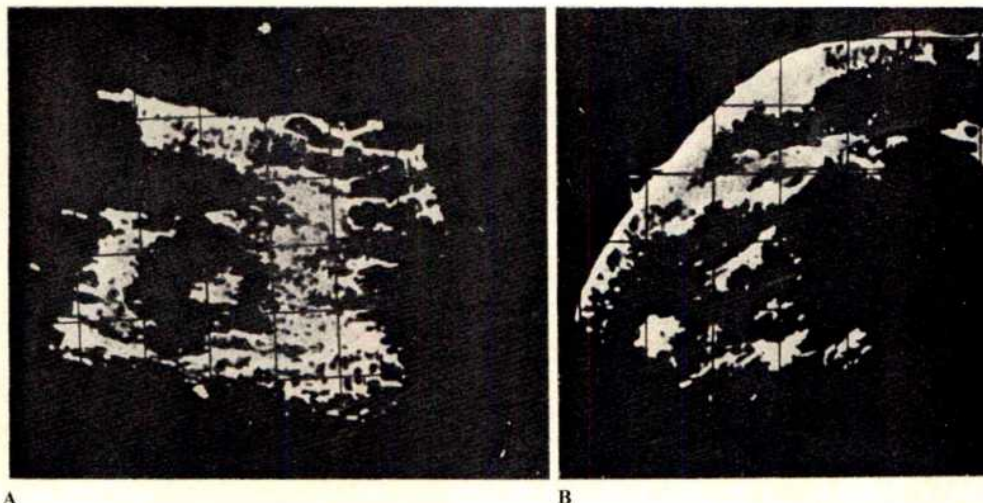


Fig. 4. (J. B.). A, Longitudinal and B, transverse scans of the left kidney in a man of 65. The kidney appears enlarged and irregular with multiple echoes arising from within it. This was interpreted as tumour but did in fact represent multicystic disease.

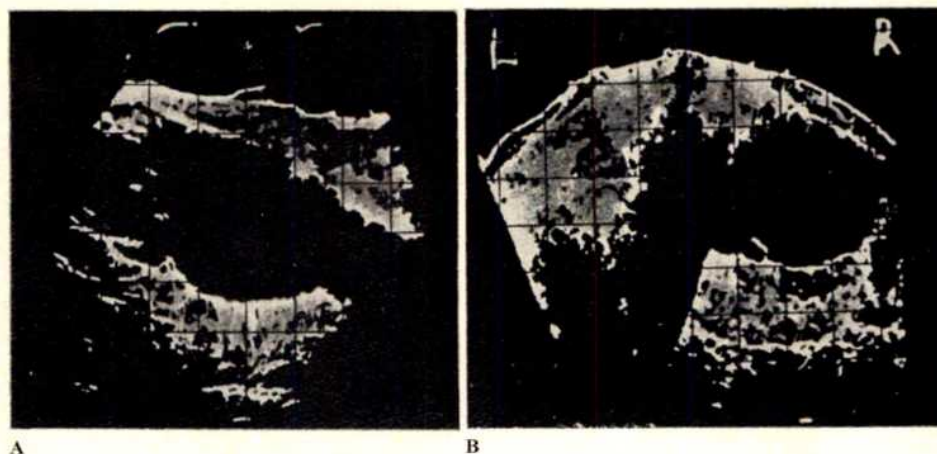


Fig. 5. (I. C.). A, Longitudinal and B, transverse scans. These scans show a large transonic mass in the area of the right kidney. This was interpreted as a hydronephrosis instead of a perirenal abscess. In retrospect, the echoes seen in a central superior position on the longitudinal scan probably arise from the pelvi-calyceal system and might have given a clue.

on the right side. Ultrasound showed a large transonic mass, diagnosed as a hydronephrosis, which was punctured (Fig. 5). This proved to be a large perinephric abscess resulting from rupture of the renal pelvis in association with calculus obstruction.

Finally there were 3 patients who had a space-occupying lesion on urography where the sonogram failed to show the mass. Puncture in each of these patients showed a cyst with a capacity of between 20 and 30 ml.

Patients in whom the sonogram gave no useful information

In 1 patient who presented with haematuria and had a normal urogram, we were unable to demonstrate the kidney under the left costal margin.

Discussion

In 61 studies where a definite opinion was expressed from the sonar findings and the final true situation was known, the accuracy rate was 87%. The 8 misdiagnoses were: One missed hypernephroma, 1 missed renal pelvic tumour, 1 small kidney diagnosed as a hydronephrosis, 1 multicystic kidney diagnosed as a tumour, 3 solitary cysts missed, and 1 perinephric abscess diagnosed as a hydronephrosis.

It cannot be over-emphasised that ultrasound should not be used as a solitary diagnostic test but as a means of deciding whether the next stage is a puncture, an arteriogram or an exploration. Thus the situation in 4 of our patients whose sonograms showed a cyst but in whom no further procedure was carried out is unsatisfactory and it is only because these patients were so ill that they were left without further investigation.

Because a further procedure is necessary the accuracy rate is not of paramount importance. The worst that might have happened in this series would have been a puncture of the kidney containing tumour which we diagnosed as cystic. There is little, if any, evidence that this alters the prognosis. Barnett and Morley (1972b) warn that ultrasound is not a satisfactory method of showing renal pelvic tumours and we certainly failed to show such a tumour, although it was obvious on an excretion urogram. The misdiagnosis of a tumour for a multicystic kidney in an adult is not a serious mistake as if it is non-excreting it would need to be removed anyway. For simple cysts to be diagnosed they need to be over a certain size. We missed 3 cysts between 20-30 ml whilst all the cysts which were confidently diagnosed were over 50 ml.

Finally our diagnosis of a perinephric abscess as a hydronephrosis was incorrect. This lady had a stone in her ureter and the renal pelvis had spontaneously ruptured to give a large collection of infected urine around the kidney. Our interpretation was, no doubt, flavoured by our clinical impression of the case at the time, and the finding of a huge transonic mass which we felt was consistent with a hydronephrosis.

Because only 1 in approximately 20 renal masses found at excretion urography is a carcinoma, it is highly desirable to avoid surgical exploration in each case with its associated morbidity and to keep the investigations as safe and simple as possible but maintaining maximal accuracy.

Mountford *et al.* (1971) suggested that transonic lesions should be punctured under X-ray control and apparently solid lesions examined by selective renal angiography. In this small series we avoided an arteriogram in 23 patients. In the vast majority of patients who are found to have a renal mass, a diagnosis can be made by excretion urography with nephrotomography, followed by ultrasonic examination, and, if cystic, puncture under local anaesthesia. In this way, the patient is spared arterial catheterisation, general anaesthesia and surgical exploration. Admission to hospital is necessary for 1 night only following a renal cyst puncture.

Finally in the symptomatic patient with a normal I.V.P. we have found that ultrasonic examination has added little, if anything, to the diagnosis. This is in line with the views of other authors who consider that the main contribution of ultrasound is in the management of surgical problems of the kidney.

Summary

Ultrasound has proved to be a useful and practical additional tool in the routine examination of patients with renal masses or unilateral absence of renal function. In our hands it has been 87% accurate and by combining it with cyst puncture, we have avoided arteriography, general anaesthesia and surgical exploration in the majority of our cases with cystic lesions. We feel

that it has no place as an isolated investigation for an instant and infallible diagnosis, but must be followed by a further diagnostic procedure whether it be a cyst puncture, arteriogram or a surgical exploration.

We wish to thank Mr G. C. Tresidder and Professor J. P. Blandy for allowing us to publish details of patients under their care.

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Treatment of Renal Adenocarcinoma by Embolic Occlusion of the Renal Circulation

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Spontaneous regression of metastasising renal adenocarcinoma has been described by several authors including Bartley and Hultquist (1950), Ljunggren *et al.* (1959) and Everson and Cole (1966). It has been postulated that the regression of metastases occurs more readily when there is widespread necrosis of the primary tumour (Sophocles and Nadler, 1971). In 50% of cases with renal adenocarcinoma a specific immune response can be shown (Stjernswärd *et al.*, 1970). If the total amount of tumour tissue can be reduced by, for example, surgical removal or the production of necrosis of the primary tumour, the immunological action on the metastases may be facilitated.

With this in mind we have developed a safe and simple technique for occluding the renal circulation experimentally in animals, thus producing a widespread renal necrosis (Almgård and Ljungqvist, 1971). Our aim was to develop a method which could produce necrosis in a carcinomatous kidney and consequently lead to (i) a reduction of the total body tumour mass, (ii) a facilitation of surgery upon large vascular tumours and (iii) a reduction of troublesome haematuria.

Patients and Method

19 patients with renal adenocarcinoma were treated. In 11 of these metastases were demonstrated preoperatively: in 8 cases in the lungs, in 2 in the skeleton and in 1 in the vagina. In 3 more cases local metastases were found at operation.

In all patients fine needle biopsy was performed preoperatively in order to determine the grade of malignancy of the tumour (von Schreeb *et al.*, 1967). This showed 5 cases of poorly differentiated, 8 of moderately differentiated and 6 of highly differentiated tumours.

The indications for occlusion treatment were: in 11 cases a large metastasising tumour, in 4 cases a large tumour without metastases and in 4 cases troublesome haematuria. The method developed in animal experiments (Almgård and Ljungqvist, 1971) was used. For this, muscle pieces sized $2 \times 2 \times 2$ cm were taken from the patients' own quadriceps and the whole mass finely minced to give a total volume of 3-5 ml. The "meat balls" were then suspended in a few ml. of physiological saline and then injected with 60% contrast medium into the renal artery (Fig. 1), after renal artery catheterisation the total volume injected being 15-20 ml. The injection was carried out under television control. In 11 cases 10-20 ml of 30% glucose was further added after the injection of the suspension. General anaesthesia was not necessary.

In 9 instances the injection therapy was followed by surgical removal of the kidney 10-42 days later. Numerous pieces were taken from both the tumour and other parts of the kidney and processed for histological examination. The sections were stained with haematoxylin-eosin, van Gieson's connective tissue stain and Ladewig's stain for fibrin. In 4 instances the histological examination was combined with stereo-microangiography for an evaluation of the effect of the injection therapy on the intrarenal vasculature, including that of the tumour (Ljungqvist, 1963;

Ljungqvist and Lagergren, 1966; Almgård and Ljungqvist, 1971); in the other 5 surgical specimens microangiography was unsuccessful due to difficulties in cannulating the extrarenal arterial branches for the contrast injections.

Results

All the patients had a mild fever for the first 24 hours following the injection. Several patients developed a moderate degree of pain and tenderness over the kidney during the first 2 days after the injection, but in only 2 of these were analgesics required. In the 4 cases with troublesome haematuria this symptom *gradually* disappeared over 1 to 3 days after the injection. There

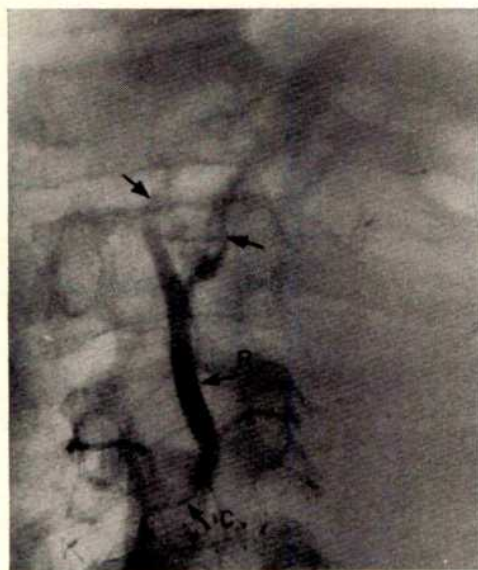


Fig. 1. Selective renal angiography after embolic occlusion of the renal vessels which are displaced upwards. The picture is taken at a late phase of injection. C = catheter in renal artery (R). In both large arterial branches several muscular emboli are seen (arrowed.) The slow passage of contrast medium is caused by obstruction in the main renal vessels. (Wire sutures inserted at splenectomy 10 years previously also seen.)

were no cases of thrombosis in other arteries than in the kidney and none of the patients developed hypertension.

In 8 instances the injection therapy was not followed by operation; in 6 patients because of widespread metastases and in 2 because of their poor general condition. Five of these 8 patients died of their primary disease, 1, 2, 5, 6 and 12 months after the injection, but the remaining 3 are still alive 5, 11 and 26 months later with unchanged metastases in 2 cases and with slight progress in 1.

In 2 cases attempted nephrectomy after injection therapy showed widespread local growth of the cancer into the liver and inferior vena cava but without distant metastases. The kidney was not removed in these patients but both are alive 9 and 10 months after the injection therapy.

In the 9 patients in whom the injection therapy was followed by nephrectomy the results were as follows. In 5 of these cases metastases were present preoperatively; in 3 patients in the lungs, in 1 in the left humerus and in 1 in the vagina. Death ensued in the 2 latter cases 8 and 13 months postoperatively. The 3 patients with pulmonary metastases are alive 12, 13 and 20 months after nephrectomy. In only 1 of these cases has there been some progress of the pulmonary metastases. Of special interest is 1 of the 2 other patients who, prior to the injection therapy, was in poor condition with anaemia, high (110 mm in 1 hr) erythrocyte sedimentation rate (ESR), bilateral pulmonary metastases and a melon-sized renal tumour (Fig. 2). Widespread necrosis of tumour and kidney parenchyma with hardly any signs of vascularity was found at operation; this was

verified microscopically (see below). 20 months later the patient has no anaemia, the ESR is normal, the pulmonary metastases are unchanged, and the general condition is good.

In 4 patients no metastases were found at nephrectomy. One of these died of a coronary thrombosis 5 months later without any signs of cancer at necropsy. The remaining 3 patients are alive and well 4, 19 and 25 months after operation and have neither signs of residual tumour, nor metastases.

Widespread necrosis in the kidney and tumour could be seen in the surgical specimens with the naked eye. This was verified by microscopical examination of sections from both tumour and renal tissue. A certain amount of fibrosis was seen in and around the necrotic areas, but greater or smaller areas of unaffected tissue were also found. Corresponding to the necrotic areas both large and small vessels contained thrombi which totally or partially occluded them (Figs. 3 and 4). These thrombi stained heavily positive for fibrin but occasional muscle fragments were encountered. In certain areas of the larger thrombi fibrotic organisation was evident.

In all 4 cases in which histological examination was combined with stereo-microangiography there was necrosis, and this was particularly extensive in 1 case. In this, the specimen showed

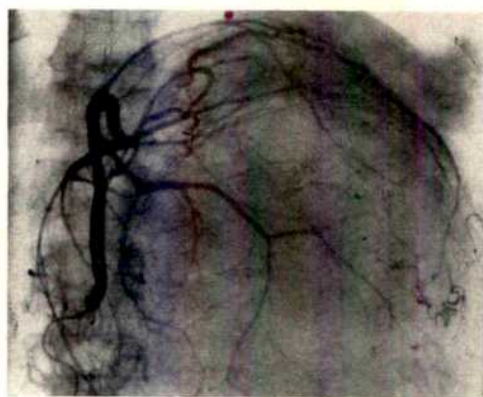


Fig. 2. Selective renal angiography showing a large tumour in the lower pole of the kidney with displacement upwards of the remainder of the kidney.

very sparse vascularity in the microangiograms. The tumour-free part of the kidney showed a more or less normal vascularity only along the cortico-medullary border, whereas the remainder of the cortical and medullary zones was avascular and necrotic (Fig. 5). The tumour itself contained avascular, necrotic areas as well as dispersed networks of sinusoidal anastomosing vessels previously described as type IV of renal tumour vascularity (Ljungqvist and Lagergren, 1966). In these regions polymorphous tumour cells were arranged in irregular tubular patterns indicating a moderately differentiated carcinoma.

Microangiography in the 3 other cases showed pictures basically similar to that described above, but the avascular areas were less extensive and in the non-tumorous parts of these kidneys both cortical and medullary areas with normal vascular patterns occurred. Within the tumours were seen areas of both finely branching vessels (type I of renal tumour vascularity) and of larger sinusoidal vessels (type IV). Histologically the type I areas showed an alveolar arrangement of monomorphous, typical hypernephroma cells of a highly differentiated degree, whereas the type IV areas showed a more tubular arrangement with a moderate degree of differentiation.

Discussion

Lalli Peterson and Bookstein (1969) developed a technique for the production of thrombotic occlusion of the pulmonary and renal circulation using Sephadex (a modified dextran composed of cross-linked macromolecules of polysaccharides). The method gave, however, a high frequency



Fig. 3



Fig. 4



Fig. 5

Fig. 3. Histological section of non-tumorous part of surgical specimen removed 10 days after injection therapy. A large intrarenal artery is longitudinally sectioned (*between arrows*). It is completely occluded by a fibrin thrombus. The surrounding renal parenchyma is necrotic. Ladewig's stain. $\times 140$.

Fig. 4. Histological section of non-tumorous part of surgical specimen removed 10 days after injection therapy. One small intrarenal artery contains a fibrin thrombus (*larger arrow*). The surrounding parenchyma is necrotic and contains 2 glomeruli (*smaller arrows*) the tufts of which are occluded by fibrin thrombi. The border between necrotic (lower part of picture) and non-necrotic (upper part of picture) tissue is fairly sharp. Ladewig's stain. $\times 140$.

Fig. 5. Microangiogram from non-tumorous part of surgical specimen removed 42 days after injection therapy. There is a normal vascular pattern along the cortico-medullary border (middle zone of picture) whereas avascular areas are seen above (cortex) and below (medulla) this zone. In the histological sections these areas showed necrosis. $\times 30$.

of complications. Lang (1971) used radioactive gold in advanced cases of renal and pelvic tumours in an attempt to obtain simultaneous necrosis and radiotherapy of the tumour tissue. Robles and Carrasco-Zanini (1968) and Sedzimir and Occleshaw (1967) treated arteriovenous malformations in the carotid region by occluding the vessels with a suspension of muscle tissue and it was this report which stimulated us to develop a technique of occluding the renal circulation in dogs (Almgård and Ljungqvist, 1971). These experiments suggested that the method could be safely applied in the treatment of patients with large renal cancers.

In the present series of cases no serious complications occurred and none of the patients developed hypertension in spite of multiple renal infarction. At the time of operation the tumours were greatly reduced in size which permitted a technically easier operation than was forecast when the patient was first examined. This shrinking of the tumour was presumably due to reduction in circulation which was observed by the surgeon in all the cases operated upon.

Histological examination of the specimens verified in most cases a marked degree of thrombosis in the blood vessels of both the tumour and the adjacent renal tissue, and widespread necrosis was seen in both the tumorous and non-tumorous parts of the specimens. Necrosis of the tumour tissue is a well-known feature also in untreated renal cancers, but most tumours of the present study displayed a more extensive necrosis than is usual. Moreover, necrosis in the normal kidney parenchyma does not normally occur in kidneys with hypernephromas but it was constantly seen in the experimental animals during the development of the injection therapy method (Almgård and Ljungqvist, 1971). Obviously therefore the injection therapy had caused the desired infarction in the present material but its extent depended on how far out in the vascular tree the thrombosis occurred. Neither in the experimental animals (Almgård and Ljungqvist, 1971) nor in the present series of human cases was a total necrosis of the kidney produced by the injections, apparently because of collaterals via the renal pelvic and ureteric vessels (Moses and Schlegel, 1952).

It appears from the present study that the widespread thrombotic occlusion of the renal and tumour vessels with consequent tissue necrosis led to at least 2 clinically favourable effects: (i) the affected kidney became more accessible to surgery and (ii) haematuria disappeared. The number of cases is, however, still too small and the follow-up periods too short to permit of an evaluation of any effect on the prognosis of the injection therapy as such. So far no cases of regression of the earlier seen metastases have occurred. In 3 cases in which injection therapy was followed by nephrectomy the metastases have remained apparently dormant 13, 20 and 26 months after nephrectomy, and in 1 of these cases there has been a clear improvement of the general condition of the patient with return of the ESR and Hb to normal levels. The period during which the metastases have remained stable in these 3 patients is surprisingly long in comparison with the earlier experience of von Schreeb (1967). The mechanism behind this hibernation of the metastases is obscure and investigations of this phenomenon continue.

Summary

An autologous muscle suspension mixed with contrast medium and injected via a catheter into the renal artery produces a partial thrombosis in the renal vessels with subsequent tissue necrosis. When applied to human cases of renal adenocarcinoma this technique produced a reduced vascularity and widespread necrosis of the tumorous kidney with an appreciable reduction of its size. Troublesome bleeding ceased and tumours became more accessible to surgical removal. In addition, the findings in a limited number of patients with metastasising renal adenocarcinoma suggested that injection therapy followed by nephrectomy may have a favourable effect on the further course of the disease.

The technique was free from any serious complications and secondary hypertension was not observed.

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Solitary Crossed Renal Ectopia

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Crossed ectopia of a solitary kidney is a very rare anomaly. Tanenbaum *et al.* (1970) reviewed 15 cases in the world literature including 1 of their own. Two of these cases had been investigated by arteriography. A further case of this anomaly, with arteriographic studies, is reported.

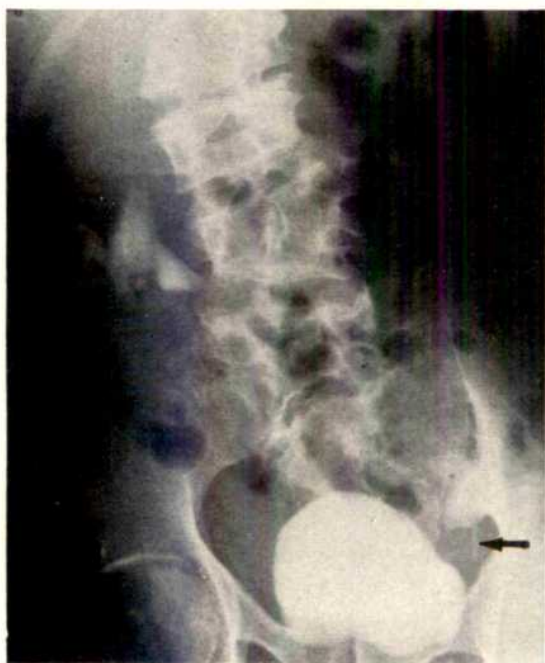


Fig. 1. Excretion urography shows a solitary kidney on the right side. The ureter crosses the midline to enter the bladder on the left side (arrows). Congenital fusion and hemivertebrae in the lumbar spine are also shown.



Fig. 2. Aortogram demonstrating the vascular supply to the solitary kidney arising from the aorta at the level of the lowest thoracic vertebrae segment. There is no renal artery on the left side.

The patient was a 50-year-old Negro who presented with rheumatic heart disease and a palpable right kidney. Excretion urography showed a solitary kidney in the right flank (Fig. 1). The ureter was clearly shown to cross the midline in the lower abdomen and enter the bladder in the normal position of a left ureter (arrows). There was no evidence of a second kidney. Several fused and hemi-vertebrae were seen in the lumbar spine, and it was noted that there were 13 pairs of ribs.

Aortography showed that the kidney was supplied by a single renal artery arising from the level of the lowest thoracic vertebral segment (Fig. 2). The coeliac and superior mesenteric arteries originated at the same level. There was no evidence of a renal artery on the left side.

This case is interesting in that the vascular supply arises at an unusually high level of the aorta, whereas typically a crossed ectopic kidney receives its blood supply from the lower aorta or an iliac vessel. In both previous cases of crossed ectopia which were investigated by arteriography, the renal artery arose from the iliac vessels.

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Transient Hypertension Associated with Closed Renal Injury

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Hypertension is recognised as an occasional late complication of severe renal injury. Transient hypertension in the acute closed unilateral renal injury has received little attention. The observation that 2 consecutive patients admitted with unilateral renal trauma had a transient hypertension led to this study.

During the period 1961-71 90 patients were admitted to the Liverpool Regional Urological Centre with unilateral closed renal trauma. The patients were divided into 2 groups as described by Slade (1971): those with severe or mild injuries. The renal injury was defined as severe when the patient was shocked, the haematuria was severe or prolonged, loin haematoma was present, and in addition there was radiological evidence of extravasation of the contrast medium with calyceal deformity. The cases were defined as mild when these features were absent.

Routine nursing observations included recording of the blood pressure at least 4-hourly for the first 24 hours after admission; subsequently the blood pressure was recorded twice daily until the patient was discharged. Hypertension was defined as a persistent elevation of the diastolic blood pressure above 100 mm Hg. When hypertension was found, hospital records or the patient's family practitioner were consulted to determine, if known, the blood pressure before the injury. If hypertension was detected the patient was reviewed annually as an out-patient.

A "severe" renal injury was found in 30 out of 90 patients. None required nephrectomy and no associated pathology or long-term complications were found in this group.

Table

Transient Hypertension in Unilateral Renal Injury

Age	Sex	B.P. Before Injury	Date of Injury	Elevation of B.P.	Duration of Hypertension in Days	Present B.P.
19	M	110/70	18.9.62	140/110	21	110/80
23	M	130/90	5.2.65	150/110	30	140/90
18	M	120/80	16.5.67	160/120	50	120/80
20	M	130/80	12.10.68	150/120	26	130/85
23	M	140/80	13.5.68	160/115	12	130/90
22	M	120/80	14.11.69	150/120	12	130/80

Hypertension was found in 6 out of the 60 patients with a "mild" renal injury. The hypertension was not present on admission but gradually became apparent within 2 days after the injury. They were not transfused and the only drugs given were morphia or pethidine, prophylactic sulphonamides and occasional night sedation with barbiturates. The case histories are described below and summarised in the Table.

Case Reports

Case 1. Male student aged 19 years. Sept. 1962. Football injury to left loin. He collapsed on games field and was admitted within 2 hours with loin pain and haematuria. He was not shocked on admission. There were minimal changes on pyelography: a small peri-renal haematoma and blurring of the outline of the left psoas muscle. His blood pressure on admission was 110/70. Two years previously he had been admitted to another hospital for appendicectomy when his blood pressure was noted to be 110/70. On the 2nd day after injury it was found to be 140/110, the hypertension remained at this level for 3 weeks and gradually became normal. The blood pressure has remained at 110/80, he was last seen in the clinic in 1971. The latest pyelogram was normal.

Case 2. Male student aged 23 years. Feb. 1962. Received an injury during a rugby game and was admitted with right loin pain with clot colic and haematuria. Nine months before he had an examination for insurance purposes and the blood pressure was found to be 130/90, the same reading was obtained on admission. On the 2nd day the blood pressure was 150/110 and remained at this level for 30 days. The radiological appearances were of a large peri-renal haematoma with minimal calyceal damage. Although the patient had recurrent clot colic for the first 5 days the haematuria was not severe. He had a persistent pyrexia which like the hypertension was present for 30 days. Detailed records are not available to show if the hypertension disappeared suddenly or gradually, but the blood pressure remains at 140/90 to date. His serum creatinine and pyelogram are normal.

Case 3. Man aged 18 years. May 1967. Admitted after a football injury with right loin pain and haematuria. Two months previously he had been treated as an out-patient at another hospital and was known to be normotensive. The blood pressure on admission was 120/80. Two days after the injury he was found to have a blood pressure of 160/120. The pyelogram showed a small calyceal tear in the uppermost calyx of the right kidney, a large peri-renal haematoma with loss of the psoas shadow; the remainder of the urinary tract was normal. He complained of headache but had no visual symptoms. No abnormality was found on the chest X-ray or electrocardiogram. The hypertension was present for 50 days and gradually fell over 2 days to 120/80 and has stayed at that level. The patient had no history of pyelonephritis but there was a family history of hypertension. The serum creatinine remained normal. The pyelogram 3 years after injury is normal.

Case 4. Man, aged 20 years. Oct. 1968. Fell against the corner of a wall which produced haematuria. On examination there was an abrasion in the left renal angle, but no loin bruise. Minimal changes were found on the pyelogram. The blood pressure on admission was 130/80. His family doctor confirmed later that this was his normal blood pressure. The following day the blood pressure was found to be rising gradually. It remained at 150/120 for 26 days then over a period of 3 days fell to normal. No abnormalities were detected on repeated chest X-rays, cardiograms or pyelograms. The blood pressure has remained normal.

Case 5. Man aged 23 yrs. May 1968. Was kicked in the right loin and was admitted with haematuria. A year previously he had had a haemorrhoidectomy. At that time and on admission his blood pressure was 140/80. There was delay in excretion of the contrast medium by the right kidney and a peri-renal soft tissue shadow was noted. No gross calyceal damage was detected. On the 2nd day the blood pressure was 160/115 and remained at this level for 12 days when it gradually fell over 2 days to 130/90. The pyelogram now is normal.

Case 6. Male student aged 22 years. Nov. 1969. Was injured playing rugby. On the 2nd day of admission he developed hypertension (150/120) which persisted for 12 days. The pre-injury blood pressure was 120/90. He had a tear of the 2 upper minor calyces of the right kidney with a large peri-renal haematoma. His father, a medical practitioner, confirms that he remains normotensive.

No changes in the cardio-thoracic ratio on chest X-ray, electrocardiogram or optic fundi were found in any of the 6 men who developed hypertension. No treatment was given for the hypertension. It appeared on the 2nd day after injury and gradually fell to normal. None of the patients have become hypertensive.

Comment

Previous reports of hypertension associated with renal injury have stressed the severity of the trauma; rupture of the renal pelvis (McElroy, 1966), traumatic arterio-venous fistula (Weir and Milliken, 1968). Permanent hypertension as a late complication of renal injury is uncommon; Slade (1971) found only 1 out of 151 cases.

The temporary hypertension in these 6 cases occurred in the acute stage. The probable mechanism is unilateral renal compression by haematoma producing ischaemia and hypertension by the

Goldblatt phenomenon (1934). Its duration is similar to that of the temporary hydronephrosis noted by Slade (1971), although this complication was not found in this study. Opit (1960) in his series had 3 patients with hypertension but does not state if it was transient and related to the post-traumatic period. In all 6 patients the radiological signs did not show gross lacerations of the kidney parenchyma, but large perinephric soft tissue shadows were present with loss of the psoas outline. This suggests that vascular compression rather than extensive parenchymal injury is the cause of the renal ischaemia. Resolution of the haematoma would relieve the vascular compression. The observed timing of the onset of the hypertension, its duration and resolution is consistent with this hypothesis.

Summary

A transient hypertension was found in 6 out of 60 patients with mild closed unilateral renal trauma.

It is a benign condition, spontaneously resolving.

The pattern of the hypertension suggests that it may be caused by renal ischaemia due to vascular compression by haematoma.

I thank Mr Cosbie Ross for permitting me to study his patients, 2 of whom developed this complication.

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Embolic Occlusion of an Intrarenal Aneurysm: a Case Report

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Aneurysms of the renal artery and its branches are usually treated by various vascular surgical techniques, renal resection or by nephrectomy (Poutasse, 1970).

A method whereby the larger renal vessels can be occluded by autoembolism has been used in the treatment of a massive renal tumour with promising results (Almgård *et al.*, 1973). The use of muscular tissue as emboli in treating arteriovenous aneurysms has been described in the field of neurosurgery (Sedzimir and Occleshaw, 1967; Robles and Carrasco-Zanini, 1968), and it seemed feasible to attempt to treat a patient with an intra-renal aneurysm by a similar technique.

Case Report

A 15-year-old boy had suffered from pain in the right flank, mild headache and occasional bouts of nausea for the past 6 months. The pain had been intermittent and lasted up to 1 hour. An I.V.P. (Fig. A) showed a suspicion of an expansive process in the upper pole of the right kidney.

Arteriography (Figs. B and C) demonstrated 2 intrarenal aneurysms of at least 1 cm in diameter. There were no signs of arteriovenous anastomoses.

The artery from which the aneurysms arose was selectively catheterised following which 2-3 cm³ of autologous muscle suspension were injected, by the technique described previously (Almgård *et al.*, 1973), resulting in complete thrombosis of the vessel (Fig. D). Prior to occlusion the patient's blood pressure was 135/75 and remained relatively unchanged (125-135/70-80) during the following day. There was a moderate pyrexia of up to 39°C and pain in the right flank which required analgesics for 2 days. The urinary sediment contained an occasional red cell and hyaline casts. During the first 2 days there was marked proteinuria.

Selective arteriography was repeated 11 days after the occlusion had been performed and again 6 months later. At this time the patient was symptom free, the blood pressure was 130/80, the urinary sediment was normal and no signs of the aneurysms were found on the arteriogram (Fig. E).

Comment

In this patient, conventional treatment would most probably have involved rather extensive renal dissection with a risk of permanently affecting the renal function.

By selectively thrombosing the artery supplying the aneurysms, this risk was greatly reduced. A moderate degree of fever and pain of a similar type to that we have encountered in embolic treatment of a renal tumour (Almgård *et al.*, 1973), occurred postoperatively. Similarly hypertension did not develop after the vascular occlusion.

Summary

Treatment of a pair of intrarenal aneurysms by embolic occlusion of their blood supply with autologous muscle suspension in a young boy is described.

There were no postoperative complications and follow-up examination at 6 months showed no recurrence of the aneurysms.

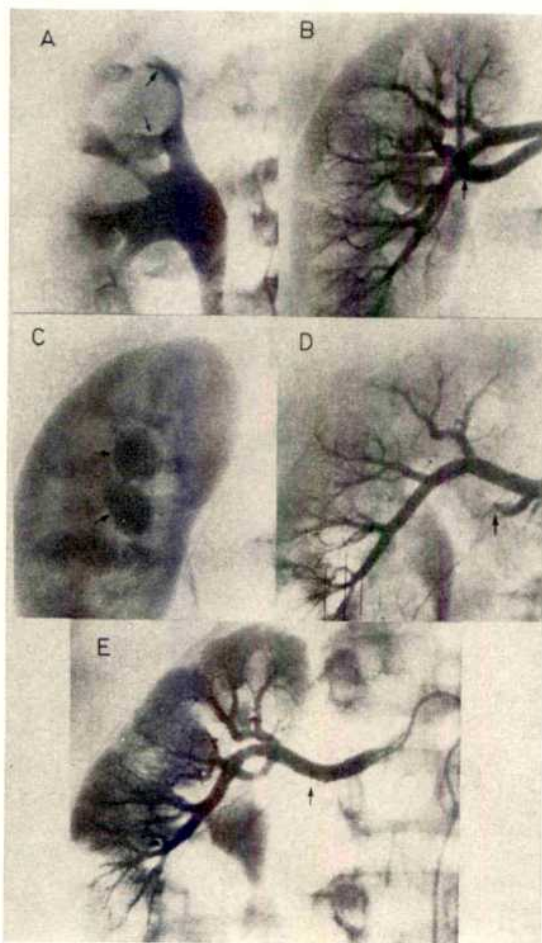


Fig. A. Intravenous pyelography demonstrating an expansive process in the upper pole on the right side (arrow).

Fig. B. Selective arteriogram of the right kidney (arterial) phase. A large artery (arrow) supplies 2 aneurysms.

Fig. C. Selective renal arteriogram (nephrographic phase). Both aneurysms are clearly shown (arrows). There are no signs of arteriovenous anastomoses.

Fig. D. Arteriogram 20 minutes after occlusion. The arrow indicates the blocked vessel.

Fig. E. Arteriogram 6 months after occlusion. The blocked artery is now patent again but very narrow. No aneurysms are seen.

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Replacement of Ureter of a Transplant Kidney with an Isolated Segment of Ileum: a Case Report

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Technical problems associated with restoration of the urinary tract continuity following renal transplantation continue to jeopardise the future of the graft. The incidence of major urological complications though variable is about 10-15% (Olsson *et al.*, 1971). Of these, fistula formation often leads to sepsis, septicaemia and at times death of the recipient or removal of the graft. Ureteric fistula that occur during the immediate post-transplant period often pose a great problem in their diagnosis and management. Various corrective procedures have been used with inconsistent results. Occasionally, after the failure of multiple attempts with further shortening of ureter, the patient is left with a nephrostomy or advised to have a nephrectomy. Isolated segments of small bowel have been used to replace the whole ureter (Goodwin, Winter and Turner, 1959; Bhat and Mohan Rao, 1969), but has not been tried in cases of renal transplant. Herein we describe a case where, after having failed with various procedures, an isolated segment of ileum was used to replace the lost ureter with success.

Case Report

M. W., 21-year-old male, with chronic glomerulonephritis and resultant chronic renal failure had been maintained on a haemodialysis programme since 30.11.1968. He received a cadaver graft on 2.4.1969. The renal artery and vein were anastomosed end-to-side to the common iliac artery and vein respectively and the ureter was implanted into

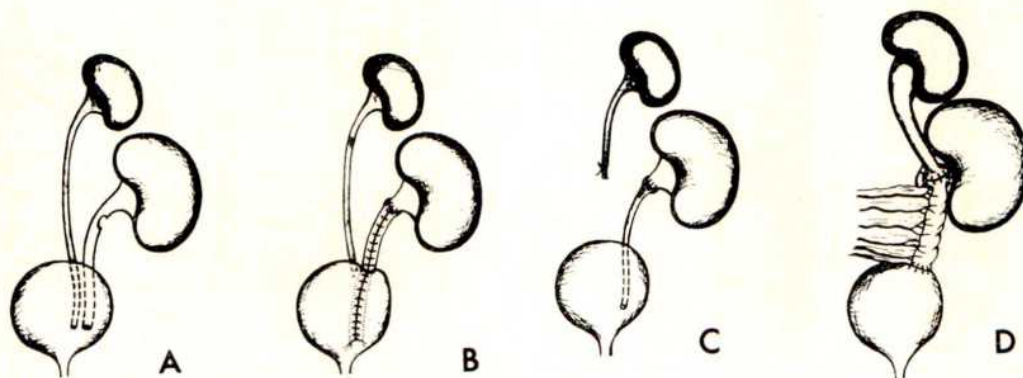


Fig. 1. A, Site of ureteric fistula. B, Boari vesical flap operation. C, Uretero-ureterostomy. D, Replacement of ureter with a segment of ileum.

the bladder, using the technique of Politano and Leadbetter (1958). Percutaneous biopsy of the kidney performed during the 24-hour oliguric period revealed no histological evidence of rejection. His urinary output was satisfactory from the 3rd post transplant day till the 8th, when there was a fall associated with an increase in the wound discharge. Urinary fistula was suspected and a ureteric fistula 3 cm distal to the pelviureteric junction was confirmed by retrograde pyelography (Fig. 1, A). This was explored on 18.5.1969 and a Boari-flap operation (Fig. 1, B) was

performed without any success. On 20.6.1969, uretero-ureterostomy (Fig. 1, c) (after ligating the patient's own ureter on the same side leaving the kidney *in situ*) was undertaken, again without success. His urine was drained through a Foley's catheter passed along the fistula tract into the renal pelvis. Since his renal function was excellent (serum creatinine 1.4 mg %) with no episode of rejection, with steroid maintenance dose of 10 mg of prednisolone per day, it was considered worthwhile to make another attempt at preserving the kidney. He was explored for the third time on 19.6.1970, 14 months after the renal transplantation. Surgical exposure of the transplant kidney was difficult because of the adhesions and the pelvis was grossly dilated with a narrow fistulous tract leading into it. The recipient's own kidney on the side of the transplant (whose ureter was previously ligated) was enlarged with a dilated and hypertrophied ureter which was adherent to the renal pelvis of the transplant and opening at the site of the fistula. A segment of ileum 4 inches long was isolated on a mesenteric pedicle, and the bowel continuity was re-established by end-to-end anastomosis. The proximal end of the isolated segment of ileum was anastomosed to the transplant renal pelvis and the recipient's left ureter while the distal end was anastomosed to the dome of the bladder (Fig. 1, d). Following this operation, his bladder was drained through a Foley's urethral catheter and the intestines were decompressed by intragastric suction. The postoperative intravenous pyelogram taken 6 months



Fig. 2. I.V.P. shows transplant kidney with ileal ureter in position.

later revealed normal size calyces and pelvis with the new "ureter" in place (Fig. 2). His renal function to date, 3½ years later, has been excellent (serum creatinine 1.2 mg %) and the urine cultures are sterile. His serum electrolytes are normal.

Discussion

Urinary fistulae that occur during the immediate post-transplant period are quite serious, because of the reported high mortality ranging from 28 % to 100 % (Olsson *et al.*, 1971). Infection which invariably follows the fistula formation is often the cause of death of the recipient, whose defensive and reparative mechanisms are deficient as a result of the high dose of steroids. Ureteric fistulae are often due to technical errors—damage to the small blood vessels that supply the renal pelvis and the upper ureter at the time of donor nephrectomy, or injury to the ureter at the transplantation (Belzer *et al.*, 1970); occasionally they may result from acute rejection of the kidney with associated similar changes in the ureteric wall (Belzer *et al.*, 1970).

Early diagnosis and a prompt attempt at surgical correction of the fistula before the super-vention of wound sepsis have been advocated by Starzl *et al.* (1970). Other methods such as temporary urinary diversion by a nephrostomy (Olsson *et al.* 1971), conservative indwelling ureteric catheter drainage (Williams *et al.*, 1970), Boari-flap operation and uretero-ureterostomy (Martin *et al.*, 1969; Williams *et al.*, 1970), have been used. When all methods failed, the kidney was removed or the patient left with a "permanent" nephrostomy.

Serum electrolyte changes have been noticed in a few cases of ileal replacement of ureter where the renal function was poor (Bhat and Mohan Rao, 1969). Because of his good renal function and the short length of ileal segment that has been used, serum electrolyte changes were not noticed in our patient.

In our experience, when major urinary fistulae occur the steroid dose should be severely curtailed; and when renal function is good with no significant rejection episodes (as in this case) every surgical means of correction of the urinary fistula should be explored before the removal of the kidney provided there is no serious infection which cannot be controlled by proper antibiotic therapy (Mohan Rao *et al.*, 1972). Short isolated segments could be used as in this case to replace the ureter lost during multiple reconstructive procedures or in the few cases of ureteral necrosis detected during the immediate transplant period.

Summary

Multiple surgical attempts using various techniques may be required to correct ureteric fistulae that occur during the post-transplant period. Though segments of ureter or whole ureter have been successfully replaced using isolated segments of ileum, this has not been tried in renal transplant patients. A successful case in which this was done with 3½ years follow-up, has been reported.

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Primary Obstructive Megaureter in Adults

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In 1923 Caulk compared an enormously dilated but apparently unobstructed ureter in a young woman to the colon in Hirschsprung's disease. He coined the word megaureter (megaloureter) to describe the condition. Subsequently the literature on the subject was confusing, as any dilated ureter was frequently called a megaureter, with distinction between refluxing and non-refluxing ureters not being made. Recently the writings of Creevy (1967), Johnston (1967, 1968) and Williams and Hulme-Moir (1970) have clarified our understanding of this anomaly, but for the most part these authors have been concerned with the appearances in children. To give a broader picture of the natural history of primary obstructive megaureter, 15 patients presenting for the first time as adults are described.

Pathology

Primary obstructive megaureter consists of a chronically dilated ureter with a short juxta-vesical segment of normal calibre, which does not reflux, and is not anatomically obstructed, but which presents a functional obstruction to the passage of urine.

The dilated ureters associated with bladder neck obstruction, stricture, neurogenic bladder, bifid ureters, ureterocoele and other congenital anomalies are not included in the definition.

The aetiology is still controversial. The neuro-muscular deficiency theory of Swenson *et al.* (1952) has been refuted (Bischoff 1961, Leibowitz and Bodian, 1963), but Kretschmer and Hibbs (1933), Murnaghan (1957) and Tanagho, Smith and Guthrie (1970) claim that an excess of circular muscle fibres in the distal segment are responsible for the obstruction. On examination of specimens removed personally, both in longitudinal and transverse section, it has been difficult to be sure that the hypertrophied circular muscle has not been the effect rather than the cause of the defect. Detection of a deficiency in the longitudinal muscle suggested by MacKinnon *et al.* (1970) has not been possible, but, as shown by Notley (1971), there does appear to be an excess of collagen tissue which may be the main pathological factor.

Whatever the aetiology there is a functional obstruction at the lower end of the ureter analogous to the pelvi-ureteric obstruction of the upper tracts.

Diagnosis

To establish the diagnosis of primary obstructive megaureter intravenous pyelography, a cystogram and retrograde assessment of the ureteric orifice are all necessary.

Pyelographically the ureter is dilated throughout its length, maximally in the lower third. It is reasonably straight with a bulb-shaped lower end. The calyces are clubbed but not as much as might be expected for the degree of dilatation of the rest of the ureter (Fig. 1). The immediate juxta-vesical segment is not usually visualised and there is marked delay of emptying of the ureter on late films. In a few patients the dilatation is not so severe, often limited to the lower third, and the end may be spindle shaped.

On screening, the ureter may show peristalsis or may be adynamic. In the latter case normal movement and flow of urine has been observed following reconstructive surgery.

The voiding cystogram is an essential investigation to exclude reflux or bladder dysfunction.

Cystoscopically the ureteric orifices appear normal and a ureteric catheter passes easily, excluding stricture, tumour or other mechanical obstruction.

Clinical Material and Presenting Features

There are 6 men and 9 women in this series. One patient had a father with a chronically dilated ureter according to the general practitioner's records, and one son had hydronephrosis due to pelvi-ureteric obstruction.

The left side was more commonly affected than the right (8 : 4), and in 3 cases was bilateral.



Fig. 1. A, Left megaureter in woman aged 37, 1962 B, Appearance 10 years later showing no significant change.

The contralateral kidney was absent in 3 patients. The lower end was spindle shaped, rather than the more classical bulb shaped, in 2 patients (Fig. 2).

The age of presentation, years under observation, and main clinical features are summarised in the Table. It will be seen that the majority of patients were first seen in their early twenties or late teens, but 4 patients did not present until after the age of 40.

Frequently the condition has come to light as an incidental finding of albuminuria, or during the investigation of vague abdominal pain. Urinary infection was uncommon, bacteria being cultured from only 3 patients. Haematuria was present initially as the main symptom in 2 patients and was subsequently reported in 2 more. Four patients had calculi.

It is noteworthy that all the patients were normotensive. Only 1 patient had a serum creatinine in excess of 1.0. The kidney of 1 woman had been completely destroyed but as judged by the intravenous pyelogram the function in the majority of the kidneys was reasonably good.

Treatment

Non-operative Regime

10 patients (see Table) have been supervised at this unit for varying periods of between 6 months and 40 years with no apparent deterioration in the status of their urinary tract as determined pyelographically (Fig. 1, A and B) or biochemically. Patients are assessed by intravenous pyelogram at 6-monthly intervals in the first year, then every 1 or 2 years on a modified basis with a 2' or 3 film pyelogram.



Fig. 2. Megaureter with spindle shaped lower ends.

Renograms are difficult to interpret but may be useful in follow-up to show significant change in function without resort to pyelography.

In a few patients there has been an occasional exacerbation of loin pain, or an isolated attack of urine infection which has responded promptly to a single course of antibiotics.

Haematuria has developed in 2 patients—in 1 of these a small stone was passed spontaneously, but in the other no cause has been found although clumps of transitional cells are present in her urine. Retrograde pyelography with screening of the ureter in various positions in this last patient has so far failed to show any sign of a tumour.

Ureteric Reconstruction and Reimplantation

Reimplantation of the ureter has been necessary in 3 patients: in 2 because of recurrent infection and in 1 because of stone formation.

A slightly modified Politano-Leadbetter (1958) technique with tailoring has been used. The ureteric orifice is circumcised transvesically and the ureter mobilised as far as possible. (A ureteric catheter sutured into the ureter during this stage of the operation is of help.) The ureter is then delivered extravesically and freed to the pelvic brim, and constructed around a 14F catheter after excising the narrow segment together with a gusset of the dilated ureter, care

Table

Summary of 15 Patients with Primary Obstructed Megaureter

Patient No.	Sex	Age of Presentation	Years Followed	Side Affected	Presentation	Treatment
1	F	31	16	Left	Pain opposite loin	Conservative
2	F	19	2	Left	Right lower chest pain	Conservative
3	M	16	5	Right*	Right loin pain	Conservative
4	F	21	40	Left	Pain both loins	Conservative
5	F	19	3	Bilateral	Albuminuria	Conservative
6	M	21	3	Left*	Albuminuria	Conservative
7	M	18	2	Bilateral	Pain right side	Conservative
8	M	55	1	Right	Calculus seen during cholecystogram	Conservative
9	M	19	6 months	Left*	Haematuria	Conservative
10	M	55	3	Bilateral	Frequency of micturition	Conservative
11	F	23	4	Right	RIF pain in pregnancy appendicectomy	Re-implantation ureter
12	F	42	4	Left	Left loin pain	Re-implantation ureter
13	F	24	2	Left	Left loin pain	Re-implantation ureter
14	F	22	3	Left	Pyelitis pregnancy	Ablation
15	F	45	1	Right	Haematuria loin pain	Ablation

* Single kidney.

being taken to preserve the blood vessels on the medial side. The redundant portion is best excised a little at a time, inserting interrupted 3/0 chromic catgut sutures at every centimetre, with a running suture along the cut surface completing the reconstruction. The ureter is brought into the bladder through a new opening and re-attached to the trigonal muscle after tunnelling it submucosally.

Results using this antireflux technique have been gratifying, with relief of symptoms, clearing up of infection and marked improvement of the pyelographic appearances (Fig. 3, A and B).

Ablation

Nephro-ureterectomy was indicated in 2 patients. The first patient presented with pyelitis of pregnancy. The kidney was non-functioning and at exploration consisted of a thin shell of tissue.

The second patient's initial symptoms were of loin pain and haematuria. Investigation demon-



A



B

Fig. 3. A, Pyelogram of 23-year-old girl pre-operatively. B, Appearance 6 months post-operatively following reimplantation of lower ureter.



A



B

Fig. 4. A, Right megaureter in patient with haematuria and loin pain. B, Repeat pyelogram 6 months after reimplantation of the ureter shows a filling defect in the middle third due to a carcinoma.

strated a megaureter (Fig. 4, A). The lower end was reimplanted. Six months later, pyelography, because of persistent symptoms, showed a filling defect in the middle third of the ureter (Fig. 4, B). At exploration this was found to be a transitional cell carcinoma of the ureter necessitating nephro-ureterectomy.

Comment

There are differences in the presentation and in the prognosis of primary obstructive megaureter as seen in the adult compared to the child.

In the vast majority of adults a state of equilibrium appears to have been reached. Infection is exceptional. In none of the patients was ureterostomy or urinary diversion required.

As might be expected, the left side was more commonly affected, as it is in children. In our small series we had more women than men, in contrast to those of Williams (1970) and Johnston (1967).

Surgical intervention has been for clear-cut clinical causes. Before the use of anti-reflux procedures results were poor, but now if recurrent infection, calculus formation or deterioration in the upper tracts are present then operative reconstruction need not be delayed. It has not been found necessary to reduce the calibre of the whole ureter as advocated by Hendren (1969) but only the part that can easily be reached through a Pfannenstiel's incision.

Examples of carcinoma in a megaureter have previously been reported by Hepburn (1962), Badenoch (1965) and Tubbs and Smith (1972). A 4th case is added here together with a patient whose urinary cytology is suspicious of neoplasia. All the reported cases were transitional cell carcinomata and it is interesting that they all occurred in the middle third of the ureter.

Haematuria in the presence of a megaureter in an adult must be investigated on its own merits and has greater significance than when it occurs in a child with the same condition. All our patients now have routine urinary cytology in follow-up in the hope that any development of malignant change will be detected early.

Summary

Primary obstructive megaureter usually presents in the adult as an incidental finding during urinary tract investigation, or with vague abdominal pain.

The condition is usually static, but if required, reconstruction and reimplantation gives satisfactory results.

Haematuria should be regarded with suspicion as malignant change may occur in the middle third of the ureter.

I wish to thank Mr N. O. K. Gibbon, Mr J. G. Gow, Mr R. M. Jameson and Mr J. Cosbie Ross for allowing me to publish the details of the patients admitted under their care. The patient with carcinoma is included by kind permission of Mr J. B. Garland of Manchester.

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The Mechanics of the Urethra and of Micturition

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This work is based on an existing approximate theory of the flow of fluid through distensible tubes and its application to micturition (Griffiths, 1969, 1971*a, b*). According to the theory the flow rate for a given bladder pressure is normally determined only by that part of the urethra proximal to a site of maximum pressure (compressive zone or elastic constriction)—which is near the mid-point of the female urethra and near the junction of the prostatic and membranous parts of the male urethra. When, as normally, frictional losses in this part of the urethra are small, the flow rate depends only on the properties of the compressive zone and the bladder pressure.

These conclusions may be understood from a simple analogy. The compressive zone is analogous to a nozzle through which fluid is forced. The flow in the distal part of the urethra is analogous to the jet of fluid emerging from the nozzle. It is common experience that what happens subsequently to the jet has no effect on the rate of flow. Similarly, that part of the urethra distal to the compressive zone has no effect on the rate of urine flow, *i.e.*, it does not contribute to the so-called urethral resistance. Thus the compressive zone controls the flow through the urethra. Further, just as the jet normally contracts to its narrowest diameter downstream of the nozzle, so the narrowest part of the urethra during flow is distal to the compressive zone and therefore has no effect on the flow rate or the urethral resistance.

The urethra may be described mechanically by specifying how the intraurethral pressure depends on position in the urethra (the urethral pressure profile) and on the cross-section of the lumen (expressed as an effective urethral radius). The pressure is due not only to passive elasticity, but also to active muscular contraction, and so will vary according to circumstances. Previously (Griffiths, 1969) the mechanical properties of the female urethra have been treated unrealistically, while those of the male urethra have been measured only distal to the compressive zone (Griffiths, 1971*b*). The present work includes data on the mechanical properties of the compressive zone both at rest and during micturition. In the first section experimental measurements of resting urethral pressure in both females and males are reported. In the following section a comparison between urethral pressures measured at rest, and bladder pressures during micturition, shows that the urethra is mechanically different during micturition and at rest. In the third section it is shown how the mechanical properties of the compressive zone during micturition may be deduced from measurements of flow rate and bladder pressure, and the conventional concept of urethral resistance to flow is criticised.

Properties of the Resting Urethra

Experimental Procedure

The urethral pressure profiles of 68 female and 33 male patients attending a urological clinic have been measured by a method similar to that of Brown and Wickham (1969). A catheter with either 1 or 2 sideholes was passed through the urethra into the bladder. Normal saline solution flowed slowly through the catheter and out of the sideholes. As the catheter was withdrawn through the urethra its position and the fluid pressure necessary to maintain the flow were

recorded on a chart. Typical records are shown in Figure 1, A and B. Many of the females complained of incontinence, which was often found to be associated with bladder instability (Bates, 1971). Many of the remainder complained of recurrent attacks of dysuria (often without proved infection). Some of the males were obstructed at the bladder neck or in the prostatic urethra and some had undergone prostatectomy or bladder-neck resection. A few appeared clinically normal.

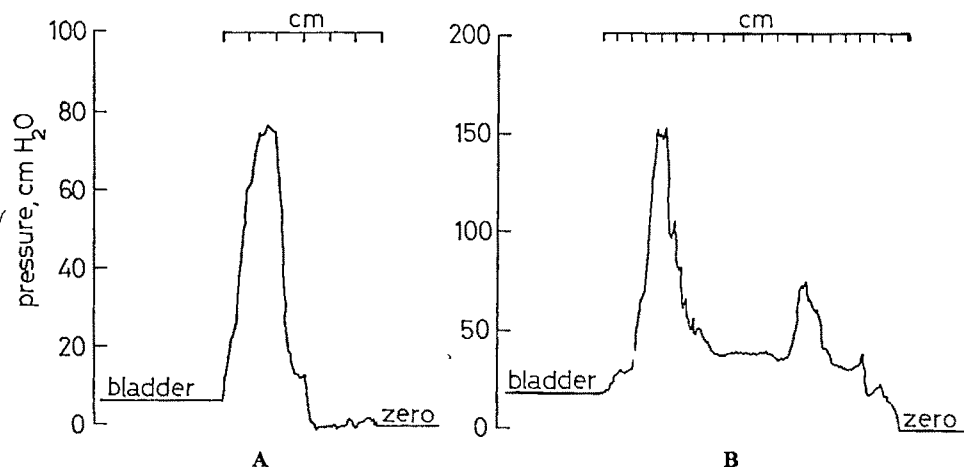


Fig. 1. Tracings of urethral pressure profiles recorded at rest in the supine position with the bladder full: A, female with unstable bladder, catheter size 12 French gauge (0.20 cm radius), B, normal male, catheter size 14 French gauge (0.23 cm radius). The cm scales record the appearance of marks on the catheter at the external meatus.

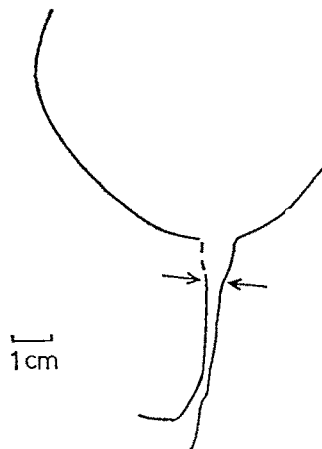


Fig. 2. Tracing of cystourethrogram of a female with unstable bladder, micturating in the standing position at a flow rate of $15 \text{ cm}^3 \text{ s}^{-1}$. The arrows show the position of the compressive zone.

The routine clinical investigation of each patient normally included also a micturating cystourethrogram recorded on cine film or videotape (Fig. 2) with a continuous superimposed record of the total bladder pressure, the rectal pressure (assumed equal to abdominal pressure), the intrinsic bladder pressure (*i.e.* total bladder pressure-rectal pressure) and the flow rate during micturition (Bates and Corney, 1971). The catheter with which the pressure profile was recorded was also used to fill the bladder with X-ray contrast medium and to introduce a small trans-urethral catheter (0.085 cm outside radius) which was present in the urethra when the pressure profile was recorded and during the subsequent micturition.

Most of the pressure profiles were recorded with the patient relaxed and supine and the bladder

filled with X-ray contrast medium to its maximum tolerable (but not painful) capacity. On some patients the pressure profile was also measured with the bladder empty, on others with the patient both supine and standing. Most of the profiles were recorded with a catheter of 0.20 cm radius (12 French gauge) but some with a catheter of 0.23 cm radius (14 French gauge). The effects of varying the catheter radius and the rate of flow of the saline solution were examined in a few patients.

Reliability of Results

With the flow rate of the saline solution in the range $1-4 \text{ cm}^3 \text{ min}^{-1}$ the pressure drop along the catheter was negligible and the response time was short enough for good resolution of the profile. In 4 patients the pressure at the compressive zone was almost unaffected by changes in the saline flow rate between 1 and $4 \text{ cm}^3 \text{ min}^{-1}$. Therefore it should be equal to the pressure exerted by the urethral walls at the site of the sideholes when the urethral radius is equal to that of the catheter.

The urethral pressures of 2 female patients were measured with several catheters of radii from 0.08 to 0.32 cm (5 to 19 French gauge). In both cases the pressure was almost independent of catheter size, within experimental error, just as in the male penile urethra (Griffiths, 1971*b*). This result is confirmed by James (private communication) and by the observation that the measured pressure is almost independent of the saline flow rate, for to exert a substantially higher pressure the urethra would have to be expanded by the saline solution far beyond the radius necessary to allow a flow of only $4 \text{ cm}^3 \text{ min}^{-1}$ to pass in the direction of falling pressure. The reproducibility of the results has been further checked by straightforward repetition of the profile measurements and by monitoring the maximum urethral pressure for times up to 1 min. In all these tests the measured pressures changed by less than $\pm 5 \text{ cm H}_2\text{O}$, except when the patient was asked deliberately to hold urine. Occasionally spasmodic changes in urethral pressure have been observed on a pressure profile when the patient had not been asked hold urine. In most cases however the measured urethral pressures appear to be both sustained and reproducible.

The experimental error inherent in the measurement of urethral pressure appears from previous work (Griffiths, 1971*b*) to be about $\pm 5 \text{ cm H}_2\text{O}$, and this is consistent with the above results. However, under clinical conditions errors of up to $\pm 10 \text{ cm H}_2\text{O}$ appear likely. It is estimated that the bladder and rectal pressures measured during micturition also may be in error by up to $\pm 10 \text{ cm H}_2\text{O}$.

Effect of Changes in Abdominal Pressure on the Urethral Pressure Profile

Pressure profiles have been recorded in both the supine and the standing positions for 6 females with full bladders (see Table I). In the supine position the abdominal and bladder pressures were usually very low. On standing the abdominal and bladder pressures rose by about $30 \text{ cm H}_2\text{O}$ on average. It is important to know to what extent changes in abdominal pressure are transmitted to the compressive zone of the urethra. The experimental results are shown in Table I. The mean rise in maximum urethral pressure on standing ($22 \text{ cm H}_2\text{O}$) was 73% of the mean rise in bladder pressure ($30 \text{ cm H}_2\text{O}$). Except in 1 case (where the patient suffered from an acute sense of urgency on standing and was almost certainly contracting her voluntary sphincter) the rise in maximum urethral pressure was always less than the rise in bladder pressure. This result, which is similar to that of Enhörning (1961), is consistent with the transmission of abdominal pressure changes to the urethra by mainly mechanical means, with little contribution from reflex muscular contraction. Some similar results have been obtained in males.

Urethral Pressure Profiles: Experimental Results

In 39 females in the supine position with the bladder full the mean bladder pressure was $17 \text{ cm H}_2\text{O}$ and the mean maximum urethral pressure was $86 \text{ cm H}_2\text{O}$. Because of the transmission of abdominal pressure to the urethra, the difference between the maximum urethral pressure and

the abdominal (or resting bladder) pressure is very approximately independent of the latter, and hence of the attitude of the patient and of whether he or she is straining to pass water. This pressure difference may be called the intrinsic urethral pressure or urethral closure pressure (Enhörning, 1961). The intrinsic urethral pressures of these females are shown on the abscissa

Table I

Females: Changes in Total Bladder Pressure and Maximum Total Urethral Pressure on Standing

Pressure in Supine Position		Change in Pressure on Standing		
Bladder Pressure cm H ₂ O	Max. Urethral Pressure cm H ₂ O	Bladder Pressure Increase cm H ₂ O	Max Urethral Pressure Increase cm H ₂ O	
5	100	35	10	
15	100	18	15	
10	120	30	20	
10	30	25	25	
40	86	48	18	
12	69	26	41	
Mean values	15	84	30	22

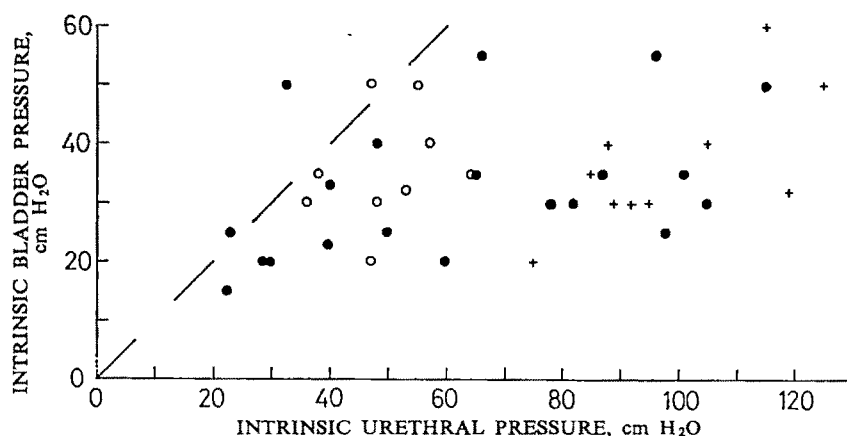


Fig. 3. Intrinsic urethral pressure measured at rest in the supine position with the bladder full, and intrinsic bladder pressure measured at peak flow during micturition, for 39 females. Crosses: continent females with history of recurrent dysuria; open circles: females with unstable bladders and no recurrent dysuria; full circles: other females.

of Figure 3. (The ordinate refers to different measurements, discussed below.) The mean intrinsic urethral pressure was 69 cm H₂O, but this value may not be typical of the normal, for Figure 3 suggests that the intrinsic urethral pressure depends on pathology. In 13 patients (not all on Fig. 3) suffering from incontinence associated with an unstable bladder, and not complaining of recurrent attacks of dysuria, the intrinsic urethral pressure had a mean value of 51 cm H₂O and a standard deviation of 12 cm H₂O. For 14 patients without symptoms or history of incontinence, but complaining of recurrent dysuria with or without proved infection, the intrinsic urethral pressure had a mean value of 92 cm H₂O and a standard deviation of 24 cm H₂O.

There is a little overlap between these 2 groups, but the mean value for the second is very significantly higher ($P < 0.001$) than that for the first. It is not clear whether the incontinent patients have abnormally low urethral pressure, or whether irritation of the urethra has led to abnormally high pressures (Tanagho *et al.*, 1971).

For the pressure profiles of 23 males, recorded in the supine position with the bladder full, the corresponding figures are: mean bladder pressure 18 cm H₂O, mean maximum urethral pressure 117 cm H₂O, mean intrinsic urethral pressure 99 cm H₂O. No association with pathology was noticed.

For 9 females urethral pressure profiles were recorded in the supine position with the bladder both empty (immediately before filling with X-ray contrast medium) and full (immediately after filling). The results are shown in Table II. In every case except one the intrinsic urethral pressure had increased after the filling, on average by 8 cm H₂O.

Table II

Females: Intrinsic Urethral Pressure in the Supine Position with Bladder Empty and Full, and Intrinsic Bladder Pressure at Peak Flow during Micturition

	Intrinsic Urethral Pressure cm H ₂ O		Intrinsic Bladder Pressure cm H ₂ O
	Bladder Empty	Bladder Full	
	73	82	30
	58	66	55
	86	96	55
	84	105	35
	140	78	35
	93	98	30
	60	100	*
	75	88	40
	37	58	*
Mean values	78	86	40

* Pressures not recorded during micturition.

Comparison of Pressures at Rest and During Micturition

During micturition the flow rate is governed by the properties of the compressive zone: *i.e.*, it depends on the difference between the bladder pressure and the pressure at the compressive zone (Griffiths, 1971a). If changes in abdominal pressure were transmitted equally to both bladder and compressive zone, they would have no effect on the flow rate. In fact transmission is unequal and they will have some relatively small effect. In an approximate analysis however only *intrinsic* pressures (measured relative to abdominal pressure) are important.

If the urethra always remained mechanically as at rest, micturition would occur as follows. The intrinsic bladder pressure would rise as the detrusor contracted, and flow would begin when it became equal to the intrinsic urethral pressure. Since the urethral pressure changes only slowly with radius, the urethra would yield readily, so that large flow rates could pass with little further increase in intrinsic bladder pressure. Hence the intrinsic bladder pressure during micturition would be approximately equal to the intrinsic urethral pressure measured at rest.

In Figure 3 the intrinsic bladder pressure at peak flow is plotted against the intrinsic urethral pressure, measured at rest with the bladder full, for the main group of females. In most cases the intrinsic bladder pressure is significantly less than the intrinsic urethral pressure. This is true also for a group of 7 unobstructed males (mean intrinsic bladder pressure 39 cm H₂O, mean intrinsic urethral pressure 97 cm H₂O). Thus, as expected, the urethra normally relaxes on micturition. Table II suggests that the intrinsic urethral pressure after micturition (bladder empty) is lower than before (bladder full) (but it still exceeds the intrinsic bladder pressure at peak flow). Thus the urethral musculature apparently contracts again after micturition, although not so much as when the bladder is full. It follows that the mechanical properties of the urethra at rest might differ completely from those that govern micturition. For example, the mid-urethral compressive zone might be abolished by urethral relaxation. In fact the shape of the urethra during micturition suggests that this is not so (Griffiths, 1969, 1971a) and measurements of female pressure profiles show that, even under curare, the compressive zone is still present although the intrinsic urethral pressure is reduced (Tanagho *et al.*, 1971).

It is possible to determine the properties of the compressive zone during micturition from suitable measurements, as shown below. In order to do so the physical characteristics of bladder and urethra and their interrelation in micturition must first be considered in more detail.

Micturition

The Bladder Output Relation

It has been argued that the main contribution to the pressure that drives the flow comes from the intrinsic bladder pressure developed by contraction of the detrusor. On simultaneous records of flow rate and bladder pressure it is striking that, when the patient is asked deliberately to stop the flow before the bladder is empty, the intrinsic bladder pressure almost invariably rises as the urethra is closed, typically by about 15-20 cm H₂O. When the flow starts again the intrinsic bladder pressure drops to near its former value. (If the flow remains shut off for more than a few seconds the intrinsic bladder pressure may begin to fall, but this is normally a slow process.) Now the tension developed by a muscle depends on its speed of shortening in a manner which is well known for striated muscles (Hill, 1938) and believed to be similar for smooth muscles such as the detrusor. When the speed of shortening is zero the tension attains its isometric value for the given muscle length and degree of activation. As the speed of shortening increases the tension in the muscle falls, reaching zero at a maximum speed of shortening characteristic of the muscle. The tension exerted at a given speed of shortening depends on both the isometric tension and the maximum speed of shortening of the muscle. Both of these in turn may depend on the length of the muscle and its degree of activation. In the bladder the intrinsic pressure depends on the tension in the detrusor and on the instantaneous bladder volume. The rate of flow out of the bladder is related to the speed of shortening of the detrusor fibres and the bladder volume. Therefore the intrinsic bladder pressure attains its isometric value at zero rate of flow. As the flow rate increases the intrinsic bladder pressure falls, reaching zero at a certain maximum flow rate, as shown schematically by curve (a) in Figure 4. This is plotted for a single instantaneous bladder volume, on the value of which both the isometric pressure and the maximum flow rate may depend. When therefore the flow is shut off during micturition the intrinsic bladder pressure rises to its isometric value. This relation between intrinsic bladder pressure and flow rate, the bladder output relation, is a property of the bladder alone. With a suitable urethra any pair of values of intrinsic bladder pressure and flow rate which satisfy it could theoretically be realised.

The Urethral Resistance Relation

For a urethra with constant mechanical properties a certain intrinsic bladder pressure is needed to pass a given flow rate. In general as the flow rate increases the intrinsic bladder pressure must

increase. The relation between them is the urethral resistance relation, which depends on the urethral properties alone. If the mechanical properties of the urethra during micturition are as discussed above, the flow rate will remain zero as the intrinsic bladder pressure rises until it becomes equal to the intrinsic urethral pressure. With further increase of the intrinsic bladder pressure the flow rate will rise rapidly as the urethra yields. Such behaviour is shown schematically as curve (b) in Figure 4. If the urethra were relaxed or tightened during micturition the urethral resistance relation would move towards the left or right of the figure accordingly.

The mechanical properties of the urethra may not be as we have postulated. However, provided that frictional energy losses occurring in the flow between the bladder neck and the compressive zone may be neglected, the mechanical properties of the compressive zone may be calculated from the urethral resistance relation and vice versa.

Flow Rate and Bladder Pressure during Micturition

The actual flow rate and intrinsic bladder pressure are fixed by the intersection of the bladder output relation and the urethral resistance relation (point (c) in Fig. 4). A change in one of these relations during micturition would cause the point of intersection to move along the curve describing the other. The direction of movement is different for changes in the urethra and changes in the bladder. Thus, if the flow rate were plotted continuously against the intrinsic bladder pressure throughout micturition, it might be possible to follow separately the changes that take place in the bladder and the urethra. In practice there is delay in the measurement of flow rate and smoothing of rapid changes, but it is usually possible to find on the record of pressures and flow during micturition a series of moments when corresponding values of flow rate and intrinsic bladder pressure may be plotted. The results in two cases are shown in Figure 5, A and B. The numbers show the sequence of the points during each micturition. Similar results have been obtained in many other cases.

Figure 5, A records the micturition of a female with an unstable bladder. Except when the flow was voluntarily shut off there is little evidence of any sharp change in urethral properties during micturition (although a steady change throughout micturition cannot be ruled out). The flow was shut off twice, giving an indication of the bladder output relation at two different bladder volumes, as shown by the broken lines. During micturition the flow rate fell monotonically, evidently because of a steady change in the bladder output relation, and a smooth curve similar to the expected urethral resistance relation ((b) in Fig. 4) was traced out, as shown by the continuous line.

Figure 5, B records the micturition of a near-normal male. The behaviour of the bladder output relation is similar to that in Figure 5, A and again a smooth urethral resistance relation is traced out.

Records have been obtained from patients who strained intermittently during micturition, raising and lowering their abdominal pressure by up to 30 cm H₂O. If abdominal pressure changes were transmitted equally to bladder and urethral compressive zone they would have no effect on the record. Since transmission to the compressive zone is less than 100%, elevation of the abdominal pressure should be equivalent to relaxation of the urethra, and the urethral resistance

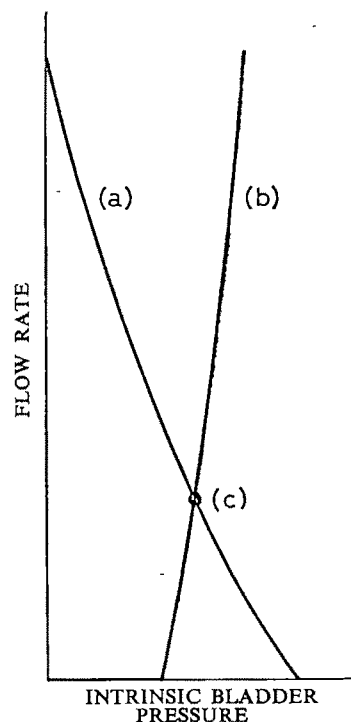


Fig. 4. (a), The bladder output relation: schematic dependence of intrinsic bladder pressure on flow rate. (b), The urethra resistance relation: schematic dependence of flow rate on intrinsic bladder pressure. (c), The flow rate and intrinsic bladder pressure as fixed by the intersection of curves (a) and (b).

relation should move towards the left on Figures 4 and 5. Unfortunately patients who strain in this way often continually alter their urethral properties by direct muscular action. In most cases, however, it is clear that changes in abdominal pressure have a small effect on the urethral resistance relation. In 1 case for example elevation of the abdominal pressure by 30 cm H₂O apparently moved the urethral resistance relation to the left by 10 cm H₂O, so that about two-thirds of the change in abdominal pressure was transmitted to the compressive zone, in agreement with the static measurements in Table I.

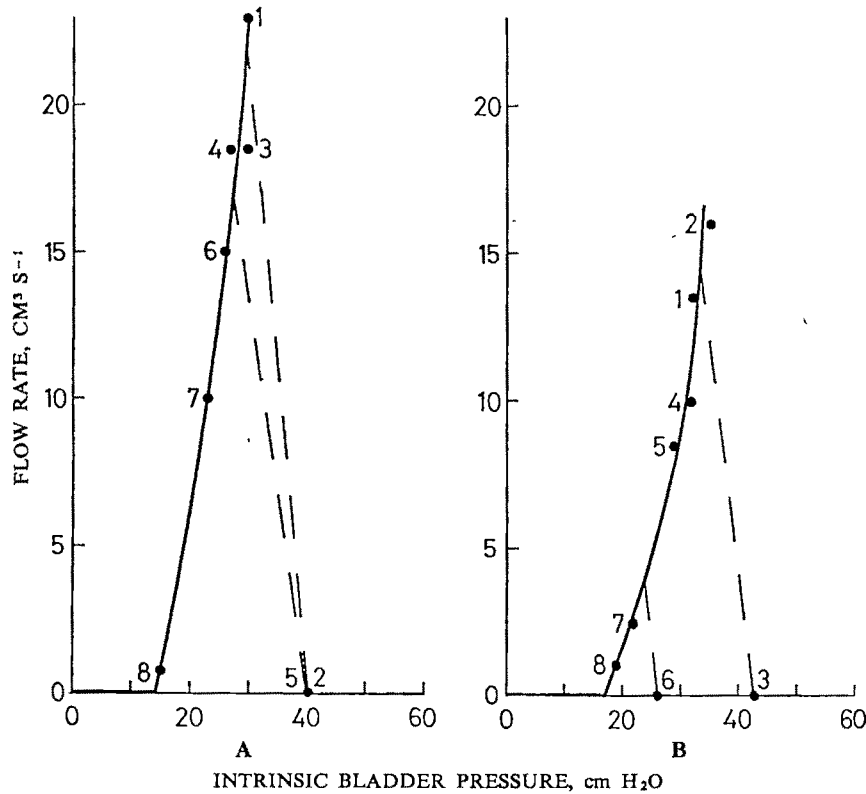


Fig. 5. Flow rate as a function of intrinsic bladder pressure during micturition. A, female of Figure 2; B, near-normal male. Full lines, apparent urethral resistance relation; dashed lines apparent trend of bladder output relation.

Mechanical Properties of the Urethra during Micturition

The smallest intrinsic bladder pressure for which flow occurs is typically of order 15-30 cm H₂O (as in Fig. 5, A) and flow rates up to 25 cm³ s⁻¹ occur with a doubling of the intrinsic bladder pressure. This behaviour suggests that, during micturition, the intrinsic urethral pressure at the compressive zone is 15-30 cm H₂O at small radius, and that the pressure increases only slowly with radius. Often little further can be deduced, but where the urethral resistance relation appears well-defined as in Figure 5, A the properties of the compressive zone may be calculated by the method given by Griffiths (1971b). In the calculation, the result of which for Figure 5, A is shown in Figure 6, the density of the X-ray contrast medium has been taken as 1.2 g cm⁻³. Frictional energy losses in the flow between the bladder neck and the compressive zone have been neglected, since this part of the urethra has wide bore. In Figure 6 the intrinsic urethral pressure increases slowly from 15 cm H₂O at zero radius to 23 cm H₂O at a radius of 0.26 cm. At 0.20 cm radius it is 18 cm H₂O. In the same patient the intrinsic urethral pressure measured at rest with a

catheter of this radius (12 French gauge) was 48 cm H₂O. Thus the magnitude of the intrinsic urethral pressure is lower during micturition than at rest, by about 30 cm H₂O. The slow variation of pressure with radius is probably similar at rest and during micturition.

Figures 2, 5, A and 6 all refer to the same female. Thus the site of the compressive zone during micturition may be found by comparing its mechanical properties with the cystourethrogram traced in Figure 2. According to Figure 6 the radius of the compressive zone at the appropriate flow rate is 0.23 cm. The scale of Figure 2 is known only roughly, the definition of the original is poor and the urethral lumen may not be circular, but clearly the compressive zone is near the position shown, where the urethra has started to funnel down from wide to narrow bore, but upstream of its narrowest part. This position, about 1.2 cm from the bladder neck, is close to that of the maximum urethral pressure at rest. In principle, by studying cystourethrograms taken

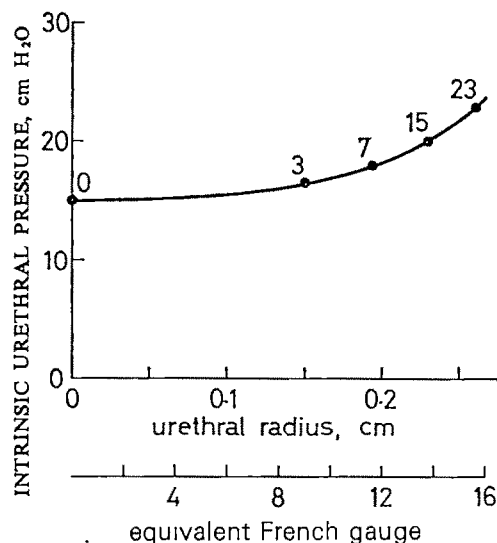


Fig. 6. Calculated properties during micturition of the compressive zone in the urethra of the female of Figure 2. The figures along the curve show the flow rates in cm³ s⁻¹ at the corresponding points.

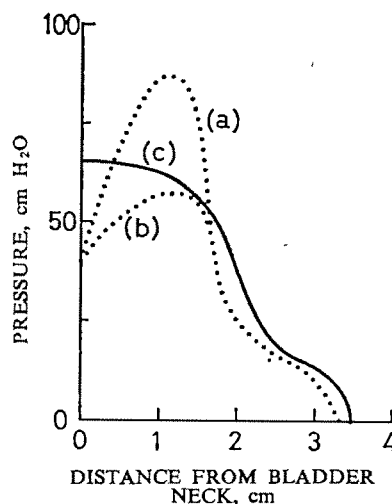


Fig. 7. Pressure distribution in the urethra of Figure 2 (a), Pressure profile at rest in the standing position. (b), Hypothetical pressure profile in the standing position with the urethra in the same mechanical condition as during micturition but with no flow occurring. (c), Actual pressure distribution in the standing position during flow at 15 cm³ s⁻¹.

at different flow rates it is possible to check whether Figure 6 is correct for the compressive zone and also to determine the mechanical properties of other parts of the urethra. In practice, as the urethra narrows the picture contrast is reduced. Nevertheless, the variation of radius at the compressive zone with flow rate and intrinsic bladder pressure appeared to be qualitatively similar to that shown in Figure 6.

The mechanical properties during micturition of the rest of the urethra are not known directly, but it is reasonable to assume that the pressure varies slowly with radius, as at the compressive zone. The magnitude of the urethral pressure at fixed urethral radius must by definition reach its maximum at the compressive zone, provided frictional energy losses are not dominant (Griffiths, 1971a). Thus, if a urethral pressure profile could be recorded with the urethra in the same mechanical condition as during micturition but with no flow occurring, the result would be as shown by curve (b) in Figure 7. This profile has been drawn as if recorded with a catheter of 0.20 cm radius (12 French gauge) in the urethra of Figures, 2, 5, A and 6. The urethral pressure profile at rest in the standing position is sketched as curve (a) in Figure 7. (It is based on the supine pressure profile.) During flow the pressure distribution is quite different from curve (b), because the urethra

is expanded upstream and narrowed downstream of the compressive zone. This pressure distribution has been calculated for the urethra of Figure 2, neglecting frictional energy losses and gravitational effects, and it is shown as curve (c) in Figure 7. It is similar to the pressure distributions measured by other workers during female micturition (Clayton *et al.*, 1966; Scott *et al.*, 1966b), which they too ascribed to a zone of high pressure acting on the urethra (*i.e.* to a compressive zone).

This account of the mechanical properties of the urethra appears to be qualitatively correct for most female urethras and for the proximal part of most unobstructed male urethras. The properties of the male penile urethra have been considered previously (Griffiths, 1971b).

Urethral Resistance and Urethral Calibration by Sounds

If the compressive zone which controls the flow were a rigid nozzle, one would find that the flow rate was approximately proportional to the square root of the bladder pressure, and could define a "urethral resistance", *e.g.* (bladder pressure/flow rate)², a single number characteristic of the urethra and independent of the flow rate. In fact the compressive zone is highly distensible, the dependence of flow rate on bladder pressure is as shown in Figure 5, A and B, and, as pointed out by Scott *et al.* (1966a), there is no obvious way to define a "urethral resistance" which will be independent of flow rate. It may be convenient clinically to calculate an apparent urethral resistance from a formula like that above, but the resulting number has no meaning theoretically.

In the past attempts have been made to assess urethral resistance by determining the largest sound which can easily be passed through the resting urethra. The results are likely to be unreliable both because the elastic properties of the urethra change on micturition and also because the variations of urethral pressure which determine the flow rate (Fig. 6) are subtle and occur at radii smaller than that determined by sounding, which is the radius at which the urethral pressure begins to rise sharply.

Conclusions

The intraurethral pressure depends both on position (the pressure profile) and on urethral radius. Pressure profiles show that at rest there is a compressive zone (pressure maximum) near the mid-point of the female urethra and near the junction of the prostatic and membranous segments of the male urethra. The mean intrinsic urethral pressure (maximum urethral pressure—resting bladder pressure) is a little higher with bladder full (mean values 99 cm H₂O for males and 69 cm H₂O for females) than with bladder empty. For females its value depends very significantly on pathology (mean values 58 cm H₂O for those with unstable bladder, 93 cm H₂O for those with recurrent dysuria). It varies only slowly with urethral radius.

During micturition the compressive zone governs the urethral relation between flow rate and bladder pressure (the urethral resistance relation). Because changes in abdominal pressure are transmitted to both bladder and compressive zone (although unequally), they have a relatively small effect on the flow rate. Hence as a rough approximation only *intrinsic* bladder and urethral pressures need be considered. The intrinsic urethral pressure is lower during micturition than at rest (by some 40 cm H₂O in females and 60 cm H₂O in unobstructed males, on average). It again increases only slowly with urethral radius. Because of this distensibility the urethral resistance relation is normally quite unlike that for a rigid tube and so it is not possible to define a simple "urethral resistance", nor is it easy to assess "urethral resistance" by passing sounds.

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Treatment of Paediatric Urinary Incontinence by Stimulator Implant

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Persistent daytime urinary incontinence in a child is both physically and psychologically disabling. The use of an implanted electronic stimulator is a well-tried procedure for resistant adult incontinence (Caldwell, 1967) and is attended by a favourable improvement rate (Table I). The

Table I
Published Records of Implant Successes

Date	Author	Number	% Success
1967	Caldwell	36	66
1968	Caldwell	9	66
1968	Alexander and Rowan	14	65
1969	Riddle <i>et al.</i>	8	50
1969	Caldwell <i>et al.</i> (children)	15	60
1970	Alexander and Rowan	29	46
1970	Warrell	5	80
1971	Edwards <i>et al.</i>	33	70
1971	Glen and Rowan	13	92

same authors (Caldwell *et al.*, 1969) treated a series of children with neuropathic bladders and achieved a 60% improvement rate. We have analysed the results in 18 children with a variety of lesions, who have been treated with stimulators after simpler measures have failed.

Patients and Procedures

17 boys and 1 girl, average age 9 years, were given stimulator implants between 1967 and 1972 at Great Ormond Street and Shaftesbury Hospitals (Table II). The electronic stimulator (Fig. 1) was made by Devices and consists of an electronic implant receiver unit, coated in medical grade silicone rubber. It is placed via a lower midline incision, in a pouch immediately beneath the anterior abdominal wall skin. A pair of platinum-iridium electrodes, covered in silicone rubber almost to their terminals, is positioned in the region of the bladder neck, where they rest adjacent to the anterior fibres of the levator ani. Initially the electrodes were placed at the bladder neck via a perineal approach. This was unsatisfactory and subsequently implants were inserted suprapubically. The implant was energised by an external flying lead transmitter which was placed over the buried implant receiver. The electrical impulses were of 5-6 volts, lasted 1-4 m.s., and were repeated at a rate of 20 per second. A full explanation of the stimulator was given to each parent and a simpler explanation was given to the child. Once the skin sutures had been removed and

Table II
Analysis of Patients with Stimulators

Initial	Age at Implant	Sex	Diagnosis	M.S.U.	Number of Previous Operations	Abdominal or Perineal Route	Follow Up	Continence
1 H. B.	8	F	Wide bladder neck	Sterile	1	Abdominal	Satisfactory	No
2 A. A.	11	M	Wide bladder neck	Sterile	1	Abdominal	Satisfactory	Yes
3 S. P.	10	M	Wide bladder neck	Infected	2	Abdominal	Long-term sulphonamides for U.T.I.	Yes
4 K. P.	11	M	Bladder neck obstruction	Sterile	1	Abdominal	Electrode extruded 2 months—stimulator re-moved	No
5 C. K.	9	M	Bladder neck obstruction	Sterile	2	Perineal	Electrode extruded 10 months—stimulator re-moved	No
6 M. A.	11	M	Epispadias	Sterile	4	Abdominal	Thigh pain—stimulator removed 11 months	Improved
7 C. S.	14	M	Epispadias	Sterile	2	Abdominal	Removed after 1 year—infection	Yes
8 G. S.	11	M	Epispadias	Sterile	2	Perineal	Satisfactory	Improved
9 S. L.	8	M	Urethral valves*	Sterile	1	Abdominal	Satisfactory	Improved
10 D. O.	6	M	Urethral valves*	Infected	1	Perineal	Electrodes fractured twice and repaired—finally removed. Further implant inserted—failed. Removed and awaiting new implant	Improved
11 N. N.	6	M	Urethral valves*	Sterile	1	Abdominal	Satisfactory	Improved
12 P. W.	4½	M	Urethral valves*	Sterile	1	Perineal	Failed: replaced via abdo. approach—failed and removed after 3 months	Improved
13 A. B.	6	M	Urethral valves*	Sterile	1	Abdominal	Satisfactory	Improved
14 K. C.	9	M	L.M.N. lesion	Sterile	2	Abdominal	Gas formation—stimulator removed after 18 months	No
15 N. C.	9	M	U.M.N. lesion	Sterile	0	Perineal	Electrodes extruding—stimulator removed after 2 months	No
16 G. F.	9	M	Dysplastic urinary tract	Infected	1	Perineal	Stimulator removed after 2 months—infection. Left ureteric re-implantation	Improved
17 L. D.	10	M	Ano-rectal agenesis	Sterile	2	Perineal	Stimulator removed after 32 months	Yes
18 C. B.	12	M	Ruptured urethra	Sterile	1	Abdominal	Satisfactory	Yes

* Post urethral valve surgery.

the wound healed, the flying lead transmitter was worn close to the skin, over the receiver. The child was encouraged to learn to do this himself and to switch the implant on and off. The child was advised to micturate every 2-3 hours during the day. If wet at night, the child was asked to wear a stimulator and to get up to micturate about 2-3 times.

The following investigations were performed: (1) History and general examination. (2) Mid-stream specimen of urine for culture and sensitivity. (3) Cystoscopy. (4) Micturating cystogram and intravenous pyelogram. (5) Urethral pressure profiles. (6) Filling cystometrogram.

The urethral pressure profile was carried out according to Harrison and Constable (1970). We attempted (but were not always successful) to measure the urethral pressure profile on the following occasions: (1) Conscious. (2) Under a general anaesthetic. (3) Under a general anaesthetic with 5 volts perineal stimulation. (4) With 5 volts perineal stimulation at operation as a guide to the positioning of the electrode.

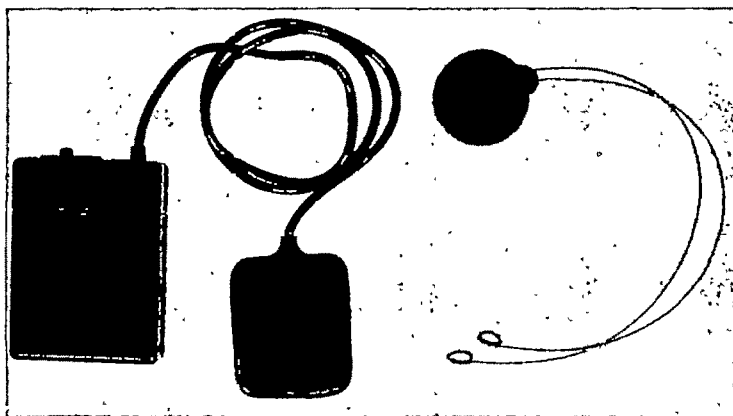


Fig. 1. Electronic stimulator and flying lead transmitter.

The filling cystometrogram was performed according to the standard technique (Stanton, 1972) without the addition of a rectal line (which was unsuitable for use in children). The cystometrogram was first performed in the conscious child and then repeated later when the child was anaesthetised (at the time of cystoscopy) in order to obtain the true bladder capacity.

Midstream Urine

Three cases were found to have recurrent urinary tract infection and were successfully treated with antibiotics or chemotherapy.

Intravenous Pyelogram

The following findings were noted: hydronephrosis, 5; pyelonephritis, 2; hydronephrosis and pyelonephritis, 1; normal, 7; untraced, 3.

Micturating Cystogram

The micturating cystogram was performed in 17 patients, and 1 attempt was unsuccessful. 12 of these demonstrated a wide bladder neck. Three were normal, 1 showed a sacculated bladder, and 1 had a small diverticulum in the posterior urethra.

Cystoscopy

Cystoscopic findings included widening of the bladder neck and trabeculation. Perineal stimulation carried out at the same time frequently produced elevation and closure of the bladder neck.

Results

There were 18 patients. Ten had had 1 previous operation for their incontinence and 7 had had more than 1 previous operation. Case 18 developed incontinence following a ruptured urethra associated with a road traffic accident and subsequently had an implant without a previous operation for incontinence. The number of previous operations did not appear to affect the success of the implant.

After insertion of an implant 13 (70%) were improved and of these 5 were entirely dry. Two cases that improved had their stimulators removed in less than a year after insertion. Five patients were left as wet as before.

Relationship to Urethral Pressure Profile

Only 8 patients had their profiles quantified. Table III shows that the highest average rise of urethral pressure on stimulation was found in the continent group and the next highest average was found in the wet group. The remaining 10 cases had an observable rise of urethral pressure on stimulation but which was not accurately measured.

Table III

Relationship of Urethral Pressure Profile to Success of Stimulator

		Urethral Pressure Profile cm H ₂ O		
		Rest	G.A.	G.A. Perineal Stimulation 5 v.
1. Continent	C. S.	20	25	90
	C. B.	...	25	175
2. Improved	M. A.	...	46	68
	G. S.	6	6	50
	A. B.	...	25	65
3. Wet	K. P.	64	35	80
	K. C.	...	30	160
	H. B.	...	35	44

Subsequent Fate of Stimulators

Seven stimulators were inserted by the perineal route. Six of these were removed—2 because of infection, 2 because of extrusion of electrodes, 1 because of repeated fracture and 1 because of malpositioning. Subsequently the stimulators were positioned via the retropubic route. Four other stimulators were removed for reasons indicated in Table II.

Extrusion of electrodes occurred in 3 patients, and in 2 patients the stimulators were removed because of infection. One case had a stimulator removed for pain.

Two stimulators failed to function although no electrical fault was found (Cases 1 and 12). The reason may have been change in electrode position or excess fibrosis developing around the electrode.

Mechanical failures were few. Case 10 had fractured electrodes on 2 occasions and fortunately the individual electrodes could be replaced without removing the receiver. Gas formation (Case 14) is rare and present stimulators avoid this problem by using a resistor across the leads.

Discussion

Two controversies arise. Firstly how the implant works and whether it produces any substantial improvement, and secondly which diagnostic procedures if any can help select the patient who will benefit by an implant. Various theories have been proposed as to how the implant works. Hopkinson (1972) writes, in relation to electronic anal plugs, that stimulation of the levator ani muscle causes a squeezing and indrawing of the anal canal. This produces both urinary and faecal continence. Alexander and Rowan (1968) question whether pelvic floor stimulation may in fact inhibit the detrusor and wonder whether the rise in urethral pressure might be due to the proximity of electrodes and fibrous tissue to the lateral aspect of the urethra. This latter concept could explain the improvement in cases 12 and 16, whose stimulators were removed at 2 and 3 months respectively. Alternatively, the theory that repetitive electrical muscle stimulation provides "daily physiotherapy" to the anterior fibres of levator ani can be considered. However, Collins, Brown and Duthie (1968) have shown no quantitative improvement in the external anal sphincter after 4 months' use of an electronic anal plug. Shelley (1969) has also pointed out that repetitive stimuli produce contractions which then diminish as fatigue sets in. Duthie (1968) has presented evidence that in order to obtain a sustained contraction, a repetitive stimulus should be applied in short bursts of pulses and not continuously.

We have found the urethral pressure profile of little value here, except that those patients who showed poor rise in pressure preoperatively were not considered for the implant. A subsequent satisfactory rise in pressure on stimulation however did not always betoken a good result (Table III). A good perineal shrug, obtained by passing a current through perineal electrodes which were positioned close to the bladder neck and anterior fibres of the levator ani was often helpful in forecasting a good result.

Cystometry was similarly used as an initial screening investigation. Those patients with a bladder capacity less than 100 ml or demonstrating a residual urine greater than 100 ml were not considered for an implant.

Alexander and Rowan (1970) when discussing their series of 29 patients treated by implants, mentioned that neither of 2 patients with a lower motor neurone type of neurogenic bladder had a good result. Harrison (1971) on the other hand, feels that an upper motor neurone lesion is a contra-indication to a stimulator implant.

Surgical Difficulties

The earlier attempts at implants were made by a simultaneous abdominal and perineal approach, because it was felt that the electrodes could be positioned more advantageously via the perineum. However it was subsequently found that this route was prone to infection and extrusion of electrodes.

Optimal positioning of the electrodes is difficult to obtain consistently. Most surgeons insert perineal needle electrodes at operation and locate the site which produces a maximal perineal shrug or a maximal and consistent rise in urethral pressure. Then via the abdominal approach, the stimulator electrodes can be brought down after dissection, to the tips of the perineal electrodes which are then subsequently withdrawn. The most successful site would seem to be on the anterior fibres of levator ani at the bladder neck. The electrodes may be sutured to adjacent fascia if they are too mobile or if there is difficulty in retaining them.

Timing of the Implant

The main consideration is that the child should be co-operative and able to help itself in the management of its condition. The youngest child in this series was 4½ years (Case 12) who seemed to cope satisfactorily, although this is younger than one might have expected. The

average age of Caldwell's series (1969) was 5 years 3 months. Several children were aged 4 years. Most children start school at 5 years of age and an effort to control their incontinence should be made at this time.

The life expectancy of the implant is about 5 years. This should provide continence up to the time of the puberty growth spurt, which may provide additional control in some of these children.

Although these children have been followed for only a relatively short time, no deterioration has been observed in the state of those upper tracts which were abnormal. A longer follow-up is necessary to be sure of this and also to determine how long the implants can usefully be expected to work.

Conclusions

It is felt that there is a definite place for the use of a stimulator implant in children with persistent urinary incontinence. The following criteria, originally stated by Harrison (1971) and now slightly modified, are suggested: (1) Satisfactory upper urinary tract. (2) Adequate bladder emptying. (3) No ureteric reflux. (4) Adequate bladder capacity. (5) Evidence of urethral incompetence. (6) Good perineal shrug in response to perineal electrical stimulation. (7) Adequate intelligence and parental cooperation.

Summary

18 children with persistent urinary incontinence were treated with a stimulator implant.

13 were improved and of these 5 were entirely dry.

The lack of a suitable investigation to aid selection of these patients is regretted.

I should like to thank Mr D. Innes Williams for allowing me to review his cases and for his help and advice in the preparation of this paper and Mr J. Nixon for allowing me to include some of his cases. I acknowledge gratefully the technical assistance provided by Mr Ken Wallace. The editor of Bio-Medical Engineering has kindly allowed reproduction of Figure 1.

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“Closed” External Sphincterotomy for Bladder Outlet Obstruction in Myelomeningocele

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It is well recognised that in adult paraplegics obstruction may occur at the bladder outlet and be responsible for dilatation of the upper urinary tract. In most cases it has been thought that the site of obstruction is at the level of the external sphincter of the urethra and the technique of external sphincterotomy by transurethral resection is widely practised with good results (Cosbie Ross, 1967).

In children with spina bifida the problems of the renal tract are partly those of associated congenital abnormalities, but mainly due to defective bladder emptying as a result of outlet obstruction. In children also it has become clear that the site of obstruction is usually at the level of the external sphincter and the technique of widening the bladder outlet by transurethral resection has been advocated in practice by Ellison Nash (1970). Although this technique can be undertaken in children there are difficulties in applying it to the small infants, and Johnston and Kathel (1971) described the technique of widening the bladder outlet in boys by a perineal urethrostomy followed by dilatation of the membranous urethra or by open division of the muscle with diathermy through the urethrostomy.

The principle of this operation is the division of the external sphincter, and the theoretical disadvantages of opening the urethra either by transurethral route or by the route of perineal urethrostomy were stressed by Zachary and Lister (1972) in describing the technique of external sphincterotomy without opening the urethra itself.

In this method the perineum is explored through a transverse incision and the bulb of the urethra exposed.

The surface of what appears to be the perineal membrane can then be cleared of fatty tissue to show the membranous urethra emerging from it. The urethra is separated from the tissues immediately posterior to it and the perineal membrane and the tissues deep to it are incised posteriorly or a wedge of tissue is removed so that the membranous urethra lies free in soft tissues. In this way it is hoped to divide the external sphincter without opening the urethra. In most of the cases under review the wound was closed completely with a catheter left in the bladder.

Patients

The operation of external sphincterotomy was undertaken in 34 male children with spina bifida. The assessment of the urological status was undertaken by intravenous pyelography, micturating cystourethrography and bladder pressure studies, and in most patients it was possible to repeat some or all of these investigations after operation.

The chief indication for operation was the presence of residual urine which could not be evacuated spontaneously by the patient and was difficult or impossible to evacuate by suprapubic pressure. In some patients with a small volume of residual urine the indication was deterioration of the upper renal tract with radiological evidence of narrowing of the urethra at the level of

the external sphincter. Of the 34 patients 3 died and 1 was not available for follow up because he had left the district.

Results

Bladder Expression (Table I). Bladder expression remained difficult in 5 of the 30 cases available for postoperative study, but was reported to be easier, either by the mother or by the examining doctor in the remaining 25.

Table I

Results of "Closed" External Sphincterotomy

Bladder expression difficult	5
Bladder expression easier	25
Died	3
No follow up	1
Total	34

Residual Urine (Table II). The volume of residual urine was assessed in 23 cases and was found to be increased in 6 cases but decreased in 8 cases and unchanged in 9. However, even in the cases where the volume of urine was found to be increased, the expression of urine was said to be quite easy in 4 of the 6 cases.

Table II

Change in Residue after Operation in 23 Cases

<i>Increased by more than 20 ml</i>	6
Expression difficult	2
Expression easy	4
<i>Decreased by more than 20 ml</i>	8
Expression easy in all 8	
<i>No change</i>	9

Table III

Radiological Changes after External Sphincterotomy

Preoperative dilatation	11	(8 with reflux)
Postoperative		
Improved		2
Unchanged		9
Preoperative reflux (without dilatation)	2	
Improved		2
No preoperative reflux or dilatation	17	
Postoperative reflux		3
Postoperative dilatation		0
Unchanged		14

Radiological Changes (Table III). There were 11 patients who had preoperative dilatation of the upper renal tract; the dilatation disappeared completely in 2 and was unchanged in the remaining

9. (Eight of these also had reflux both before and after operation.) Two patients without dilatation had preoperative reflux which disappeared completely after operation. 17 patients had neither dilatation nor reflux before operation. In 3 of these cases there was postoperative reflux but none was found to have dilatation, and 14 of the 17 had neither dilatation nor reflux after operation.

Table IV

External Sphincter Narrowing—30 Patients

<i>Present in 20</i>		<i>Absent in 10</i>	
Still present after operation	13	Present after operation	4
<i>6 deteriorated</i>		<i>6 deteriorated</i>	
4→dilated		3→dilated	
1→reflux		2→reflux	
1→increased residue		1→residue increased	
<i>9 improved</i>		<i>2 improved</i>	
2→reflux disappeared		Residue decreased	2
1→dilatation disappeared			
6→residue decreased			

Urethral Narrowing (Table IV). Narrowing at the level of the external sphincter was demonstrated radiologically in 20 of the 30 patients, and postoperative studies showed that there was still some narrowing present in 13 of these children. Nine of these 20 children had improved, in 2 the reflux had disappeared, in 1 dilatation disappeared and in 6 the residue had decreased. In 6 cases there was deterioration with increased residue or reflux.

In the 10 patients for whom the operation was done primarily for high residual urine and in whom it had not been possible to demonstrate radiological narrowing preoperatively, some narrowing was found at this level postoperatively in 4 cases, and in 6 cases out of the total of 10 the urological state of the child had deteriorated.

Table V

Cystometry—Performed Before and After Operation in 23 Patients

<i>Pressure of Contractions</i>	
Decreased by more than 15 cm water	12
Increased by more than 15 cm water	7
Unchanged	4
<i>Bladder Outlet Resistance ($\frac{P}{F^2}$) in 8 patients</i>	
<i>Resistance</i>	<i>Outlet Resistance Units</i>
Preoperative	107 172 196 250 350 361 417 666
Postoperative	30 44 12 41 82 35 70 120

Cystometric Changes (Table V). Bladder pressure studies were performed pre- and post-operatively in 23 patients. If the resistance of the external sphincter was effectively reduced one might expect the intravesical pressure measurements to be somewhat less. In a series of 23 patients the intravesical pressure was indeed decreased in 12 cases and unchanged in 4, but in 7 cases the contractions reached a higher level than before operation. Outlet resistance before and after operation

was calculated in 8 patients from the pressure and flow rate measurements using Claridge's (1966) formula:

$$\text{Resistance} = \frac{\text{Pressure}}{(\text{flow rate})^2}$$

In all of these the calculations showed that the resistance units obtained from this formula were lower after operation.

Discussion

External sphincterotomy is performed in patients with neurogenic bladders in an attempt to promote drainage and avoid deterioration of the upper urinary tract. It is a minor procedure compared with the more extensive operation of a formal ileal conduit diversion.

The main indication for external sphincterotomy in this series was a bladder residue which was inexpressible. If judged solely on this criterion only 8 cases were successful in that the residue was reduced, yet expression was easier in 25 patients even in 4 out of the 6 patients in whom the residue actually increased.

Radiological proof of improvement after external sphincterotomy by this technique was scanty, although dilatation of the upper renal tract disappeared in 2 out of 3 cases. Reflux also ceased in the 2 patients who had only this adverse radiological sign, but the operation did not prevent reflux occurring in 3 out of 17 patients with no prior radiological evidence of malfunction.

Cystometry gave some further proof of improvement after this operation. Among 9 patients with high intravesical pressure (with contraction waves more than 100 cm water) the pressure was reduced in 8. The calculation of outlet resistance from the pressure and flow readings on the basis of the $\frac{P}{F^2}$ formula also showed improvement following operation.

We must admit, therefore, that although there is evidence of some improvement in function after external sphincterotomy by this technique, the failure to cure or even to prevent malfunction in a number of children is a serious criticism. This applies particularly to children who already have both reflux and dilatation, none of whom improved.

Failure in many cases probably arises from inadequate excision of the muscle. Recent anatomical studies carried out in combination with this unit have demonstrated the thickness and extent of the muscle in children and the intimate relation that the muscle has with the mucous membrane of the epithelium of the urethral wall (London, 1972).

Following this review of our results of "closed" external sphincterotomy we are now deliberately opening the urethra just proximal to the bulb in infants and dividing the posterior wall of the membranous urethra as well as the adjacent tissues, hoping in this way to divide all the constricting fibres, whether of muscle or connective tissue. First impressions are that this technique assures better bladder emptying but a later detailed analysis will be required to compare results with those of "closed" external sphincterotomy as described here.

Summary

34 children with myelomeningocele were operated by a technique of "closed" external sphincterotomy (without opening the urethra).

Bladder expression was made easier in 25 out of 30 patients available for follow up.

The effects of operation on the volume of residual urine, reflux and dilatation of the upper renal tract were not consistent.

It is not easy to predict which cases are likely to respond to this operation sufficiently well to justify its general use for bladder outlet obstruction at external sphincter level in spina bifida.

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Observations on Urinary Chemiluminescence of Normal Smokers and Non-smokers and of Patients with Bladder Cancer

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Bladder tumours are frequently multiple, scattered throughout the bladder surface or recur at different parts of the bladder over a period of time. Furthermore they may involve other parts of the urinary tract as well. All this suggests that there might be chemical carcinogens in the urine and this is supported by the epidemiology of bladder cancer. Thus, Case *et al.* (1954) clearly showed that workers exposed to β -naphthylamine and other dyestuff intermediates were prone to develop bladder cancer. However, many cases of bladder cancer are not due to any obvious exposure to dyestuff intermediates so that other carcinogens should be sought. A correlation has been shown between cigarette smoking and the incidence of bladder cancer in the U.S.A. (Lilienfeld, Levin and Moore, 1956), in Denmark (Lockwood, 1961), in France (Schwartz *et al.*, 1961), in England (Anthony and Thomas, 1970), and in Boston, U.S.A. (Cole *et al.*, 1971). Such a correlation could operate through the occurrence of chemical carcinogens arising from the cigarette smoke and eventually appearing in the urine. Certain tryptophane metabolites known to be carcinogenic have been identified in the urine of normal individuals. The concentration of the metabolites is, however, relatively so low that the analytical problems are very great and while some have said that the metabolites are raised in patients with bladder cancer (Boylard and Williams, 1956; Price *et al.*, 1960), this has been denied by others (Benassi, Perissinotto and Allegri, 1963). Even less clear are the relative excretions of tryptophane metabolites in normal smokers and non-smokers.

A different approach may therefore be required in order to detect any differences between the carcinogenic properties of urine from normal subjects and patients with bladder cancer. The measurement of urinary chemiluminescence may be such an approach. Chemiluminescence may be defined as the production of visible or ultraviolet light during chemical reactions without apparent increase in temperature.

Anderson (1947) put forward the general proposition that the mechanism whereby chemicals act as carcinogens depends upon the chemiluminescence accompanying certain oxidative reactions. It was postulated that high-energy molecules generated during the oxidation processes could lose energy by radiation of quanta of ultraviolet or visible light and that these quanta might be absorbed by labile cell components and so lead to intracellular chemical changes which would end in malignancy. Schlegel *et al.* (1969) studied the chemiluminescence of urine and compared the results from normal smokers and non-smokers and from patients with bladder cancer. They observed a tendency for the chemiluminescence to be greater in the smokers than in the non-smokers and to be greatest of all in the cancer patients. The within-group variations were very great, however, and their between-group differences did not achieve statistical significance. No other similar study has been reported and it was therefore decided to try to confirm or refute the findings of Schlegel's group. In view of the large within-group differences reported by Schlegel, it was decided first to investigate some of the variables which might affect urinary

chemiluminescence and to try to standardise procedure as much as possible in the hope that the within-group differences would be reduced.

Material and Methods

Urinary chemiluminescence was measured by the method of Schlegel *et al.* (1969) except that all readings were made at pH 6.5 and at 25°C, unless otherwise stated, and the equipment was a Du Pont luminescence biometer to which was added a standard laboratory chart recorder. The actual measurement made was the maximum peak height after addition of H₂O₂. The instrument was standardised periodically by means of a known light source from a beta emitter. Measurements of urinary chemiluminescence were always made on the day that the specimens were produced.

Urinary ascorbic acid was measured using the Auto Analyser Indophenol method of Beyer (1967) but with preliminary removal of interfering substances by passage through a cation exchange resin (Hughes, 1964). These measurements were made within 4 hours of the passage of the urine samples.

Urinary creatinine was measured by Auto Analyser using the standard method.

Normal samples of urine were obtained from 2 sources. Firstly, laboratory workers (mainly within the hospitals) were assumed to be normal in the absence of known disease. Secondly, samples were obtained from patients attending the Grove Health Centre, London, on account of various minor ailments. Many of these patients were in fact taking drugs such as analgesics or tranquillisers, but no correlation could be observed between the drugs taken and the urinary chemiluminescence observed. Furthermore, there were no differences in results between the 2 groups of normal subjects and therefore they were pooled. Samples of urine from patients with bladder cancer were obtained from patients attending the St Peter's Hospitals mainly for follow-up and cystoscopy. The cystoscopist was asked to report on the presence or absence of cancer in the bladder at the time.

Both normal subjects and cancer patients were questioned on their smoking habits in the 3 days prior to supplying the urine samples. They were classified as smokers or non-smokers, a smoker being defined as a person who had smoked tobacco at all during the previous 3 days. 25 of the normal volunteers, of whom 9 were smokers and the rest non-smokers, gave samples of urine before and after a 3-day trial with ascorbic acid 1.5 g/day in 3 divided doses. Both urine samples were passed during the morning and examined for chemiluminescence as usual.

Results

(a) Preliminary Results on Measurement of Chemiluminescence

1. Decay with Time

Figure 1 shows the decay with time on 4 samples of urine from normal subjects on allowing the urine to stand at room temperature. There seems to be little decay in chemiluminescence up to 24 hours.

2. Effects of Dilution of Urine

Five samples of urine from normal individuals were each diluted with water in varying degrees and the chemiluminescence measured on each dilution. It was apparent (see Fig. 2) that in each case the reduction in chemiluminescence was proportional to the degree of dilution. All the lines in Figure 2 converge on a blank of about 15 units of chemiluminescence at infinite dilution and this corresponds with the water blank obtained. Hence, it is permissible to compare results from urine specimens of different concentrations.

3. *Effects of Temperature*

The chemiluminescence of 3 specimens of normal urine was studied at different temperatures ranging from about 5° to 35°C. The results are plotted in Figures 3 and 4 which show marked changes with temperature. By plotting chemiluminescence on a log scale as in Figure 4, a straight line relationship can be obtained and hence a correction made for change in temperature. In fact all measurements were subsequently made at 25°C.

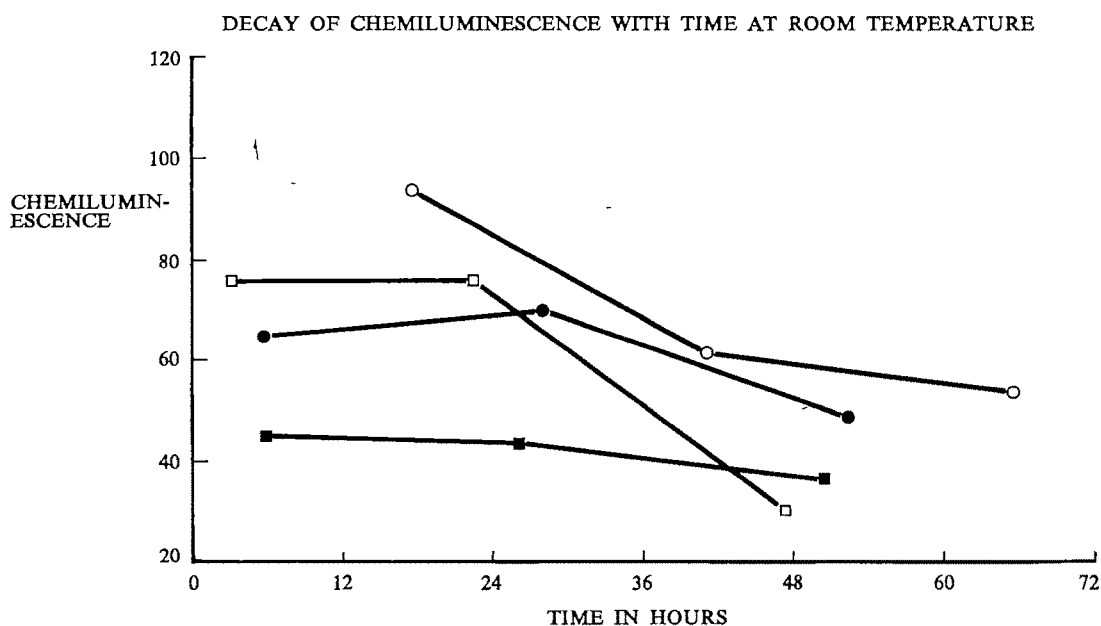


Fig. 1. Effect of time of standing at room temperature of 4 normal samples of urine upon urinary chemiluminescence.

4. *Effects of pH*

The effect of chemiluminescence of varying the pH at which it was measured from 4.5 to 9 was very great and is shown for 2 samples of normal urine in Figure 5. pH 6.5 was selected for all subsequent measurements.

5. *Effect of Ascorbic Acid Concentration*

Varying amounts of ascorbic acid were added to 8 different samples of normal urine and the effect upon chemiluminescence was studied. The results, shown in Figure 6, indicate that ascorbic acid in the urine markedly reduces chemiluminescence in both smokers and non-smokers.

6. *Effect of Blood on Chemiluminescence of Urine*

Figure 7 shows the effect of adding small but increasing amounts of blood upon the chemiluminescence of a water blank. Similar effects were found in urine and it was therefore decided to omit from the study all urinary samples which showed a positive chemical test for blood. It was found that on dialysis of diluted blood in Visking Cellophane tubing for 3 days at 4°C there was no passage of chemiluminescence across the Cellophane. This was quite different from what was found with normal urine in which the chemiluminescence was completely dialysed out under the same conditions.

(b) Results from Normal Subjects and Patients with Bladder Cancer

38 urinary samples from normal non-smokers and 30 from normal smokers were examined for chemiluminescence, creatinine and ascorbic acid levels. The distribution of ascorbic acid levels is shown in Figure 8 and it was decided to omit from the study the 5 urine samples with ascorbic acid levels above 2.5 mg/100 mg of creatinine. Urine samples were similarly studied from 26 non-smokers and 49 smokers with bladder cancer. Seven results were omitted on account of high ascorbic acid levels (see Fig. 9). In view of the effect on urinary chemiluminescence of

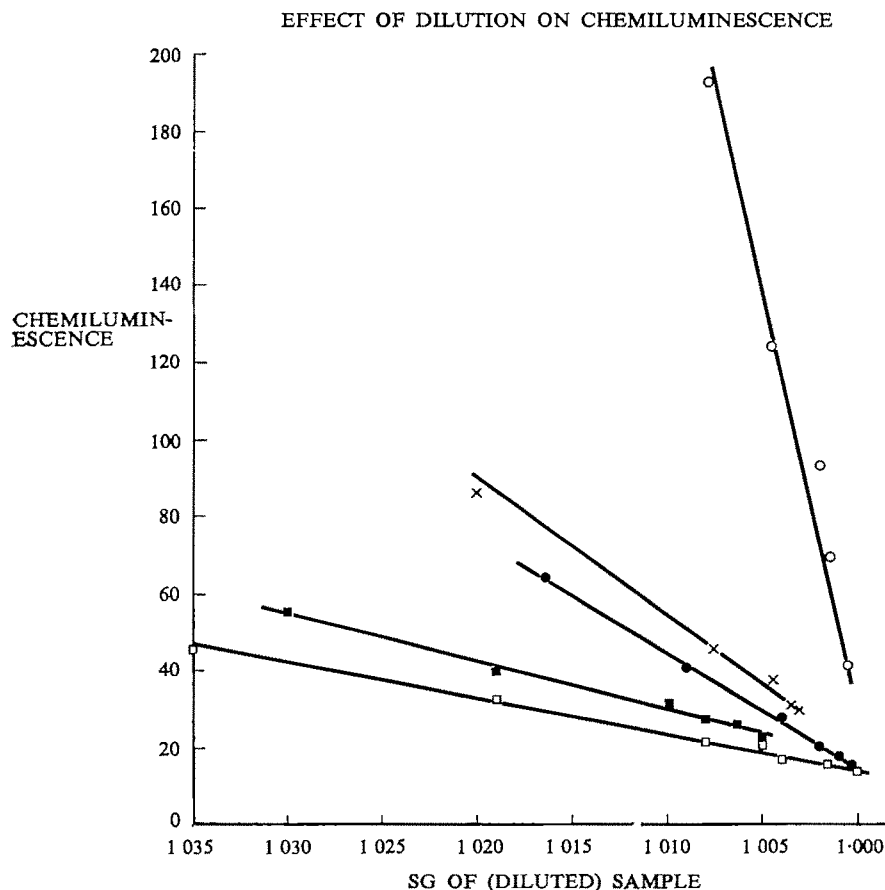


Fig. 2. Effect of serial dilutions of 5 normal urine samples upon the observed chemiluminescence.

added blood, results were also excluded when chemical tests on urine revealed its presence. The remaining results for urinary chemiluminescence and ascorbic acid content are shown in Table I. Results from smokers with cancer have also been subdivided according to whether tumour was present or absent at the time of the urine sample. These results are shown in Table II.

The effects of giving oral ascorbic acid upon urinary chemiluminescence of normal smokers and non-smokers are shown in Figures 10 and 11, and in Table IV. In each group there is a striking fall in the chemiluminescence and furthermore the values for the non-smokers continued to be lower than those for the smokers ($P < 0.001$).

Discussion

Previous reported work on urinary chemiluminescence is so scanty and so sketchy that it was felt necessary to carry out some preliminary investigations on the technique of measurement in order to make the results as significant as possible. When making a reading, urine is brought to a pre-selected pH by addition of a strong phosphate buffer and a small volume of the mixture introduced into the instrument in front of a photo-multiplier which is sealed off from all external light. At this stage a very low but steady level of light emission may be recorded. A small amount

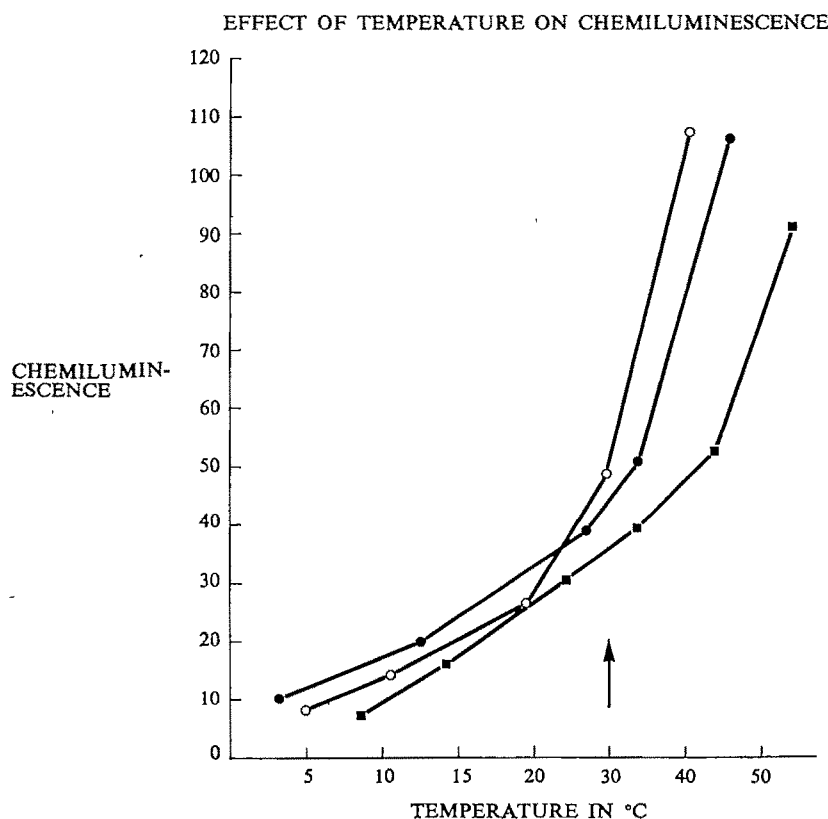


Fig. 3. Effect of temperature upon the chemiluminescence of urine from 3 different normal subjects.

of hydrogen peroxide is added through a rubber septum and this is followed by a very rapid increase in light emission which falls back towards zero in seconds or minutes depending upon the pH selected. The higher the pH, the shorter and sharper is the light emission. Attempts to standardise the instrument were made by using solutions of luminol as a working standard, but these solutions were too unstable for practical use. It was found more convenient to use a radioactive beta-emitter as a standard source of light. In practice, the sensitivity controls of the instrument required very little alteration from day to day.

If urinary chemiluminescence is dependent upon oxidative reactions, it is likely to show decay with time. Figure 1, however, shows that normal urine samples do not show significant loss of chemiluminescence within 12 hours on standing at room temperature. Urine specimens of alkaline pH might have decayed faster (see Fig. 5), but this was not investigated. Specimens were

accepted for study only provided that chemiluminescence could be measured on the same day, and provided there was no evidence of urinary infection.

Figure 2 shows that as urine samples were progressively diluted, the degree of dilution was matched by the reduction in urinary chemiluminescence. This was taken to mean, firstly that there was no detectable quenching of the light emitted in the neat urine samples, and secondly that it was permissible to adjust all the results obtained to a standard urine concentration. Since it was not possible to obtain timed specimens of urine, all results were instead related to a fixed weight of creatinine.

Figures 3, 4 and 5 show the effects of temperature and pH at which chemiluminescence was measured and these factors were therefore standardised (see above).

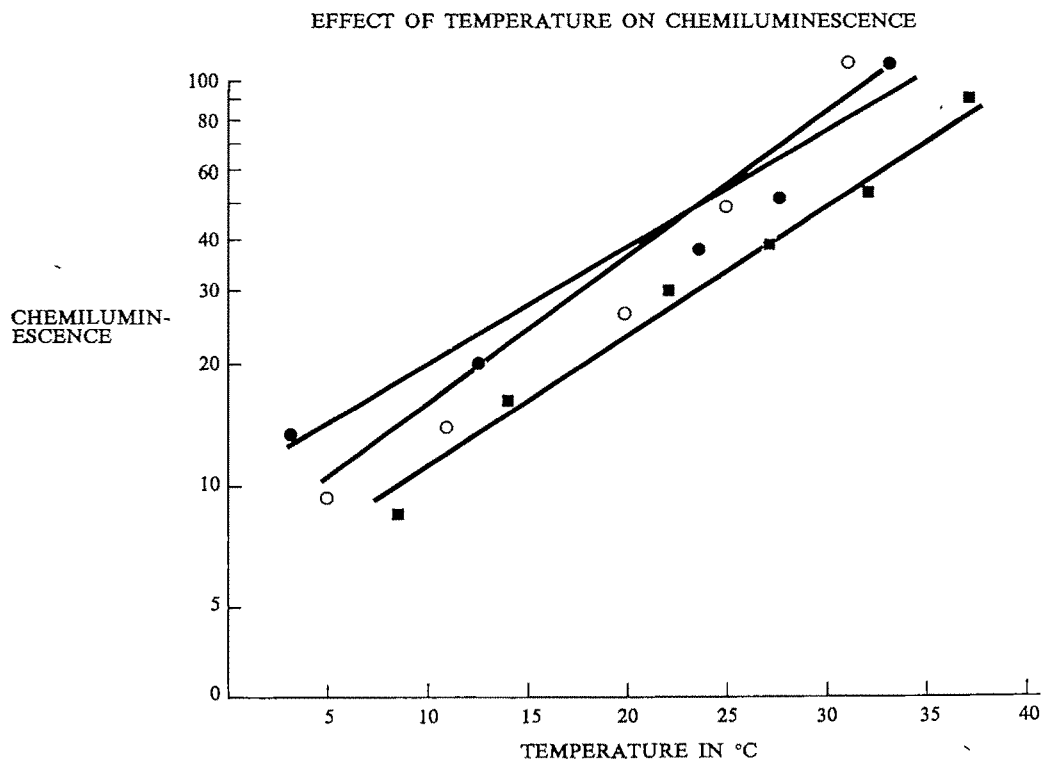


Fig. 4. The data from Figure 3 replotted using a log scale for chemiluminescence.

Figure 7 shows that traces of blood in urine could give rise to serious artefacts in measuring chemiluminescence. The possibility was considered that the whole phenomenon of urinary chemiluminescence might in fact be due to cellular constituents of blood present in urine in trace amounts. This possibility seems to have been excluded by the finding that chemiluminescence of normal urine is freely dialysible whereas that due to blood is non-dialysible across the same Cellophane membrane. It was found that the chemical test used to detect blood in urine was sufficiently sensitive to detect levels which could have given any significant chemiluminescence.

Inorganic iron and copper are known to catalyse certain chemiluminescent reactions and it was found that these ions could in fact raise the observed chemiluminescence of normal urine. However, levels of iron and copper ions sufficient to affect the results cannot occur in urine as passed and the only precaution taken in respect of these metals was to avoid subsequent contamination.

In any study of urinary chemiluminescence it is necessary to take into account the level of ascorbic acid in the urine. Firstly, it can be seen from Figure 6 that when ascorbic acid is added to urine *in vitro*, the chemiluminescence is very considerably reduced. Secondly, Schlegel *et al.* (1969) showed that after administration of ascorbic acid to normal subjects there was a large reduction in urinary chemiluminescence. It was therefore thought necessary to measure the ascorbic acid level in each sample of urine and to exclude those in which significantly raised

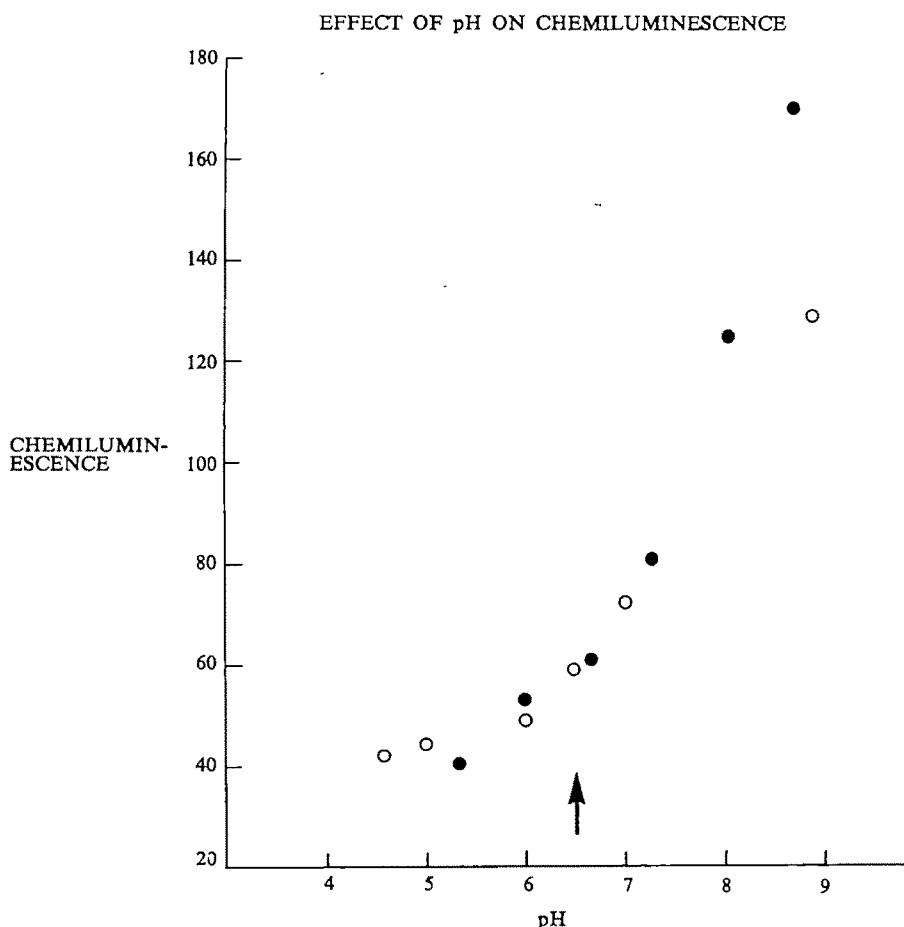


Fig. 5. Effect of final pH upon the chemiluminescence of urine from 2 different normal subjects.

levels were found. The actual levels are shown in Figures 8 and 9 and it is clear that in each group there was a small proportion with remarkably high levels of urinary ascorbic acid, and enquiry revealed that some of the patients were in fact taking high doses of ascorbic acid without the knowledge of their doctors. Where the urinary ascorbic acid levels exceeded 2.5 mg/100 mg creatinine, results were omitted from the study. In the remaining material, as can be seen from Table I, there were no significant differences between the urinary ascorbic acid of normal subjects and the bladder cancer patients, whether smokers or non-smokers. It is therefore considered that the differences in urinary chemiluminescence cannot be attributed to differences in urinary ascorbic acid levels.

When all the acceptable results for urinary chemiluminescence were studied and divided into 4 groups, mainly normal smokers and non-smokers, and smokers and non-smokers with bladder cancer, it was observed that in no group was there a Gaussian distribution of results. Such distribution could, however, be obtained if the results were plotted on a log scale. Therefore, in order to calculate S.E.M.s and *t* tests, the results were all converted to the log mode. It can be seen in Table I that differences were observed between the groups. Thus normal smokers have

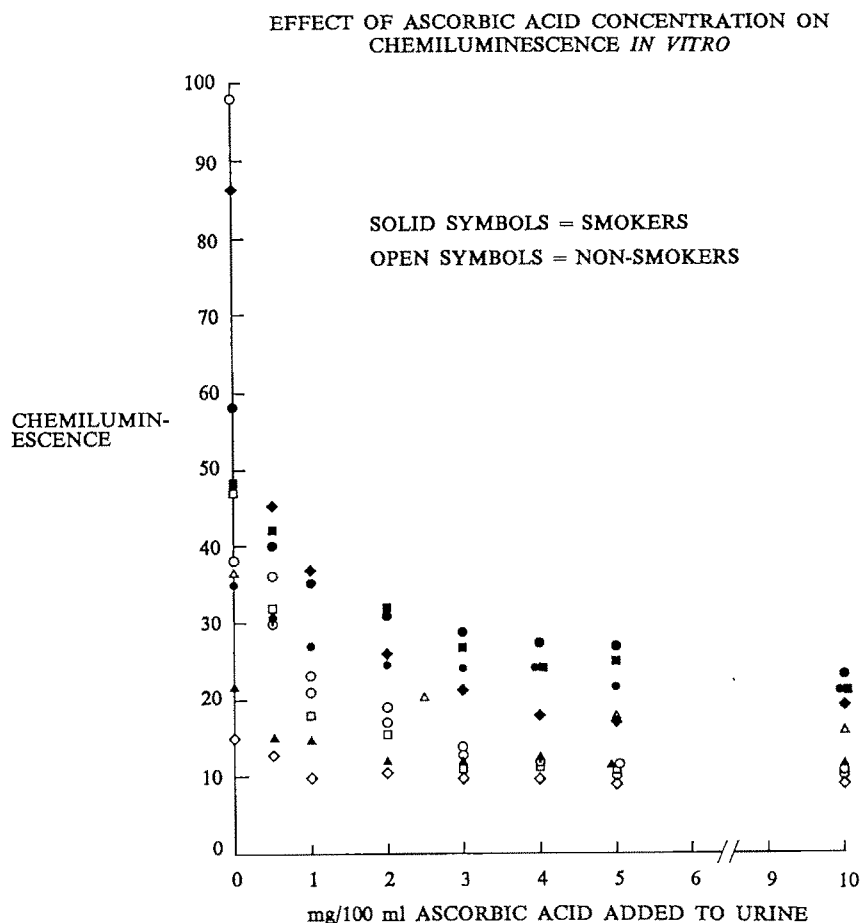


Fig. 6. Effect of adding increasing amounts of ascorbic acid *in vitro* to 9 samples of normal urine from 5 non-smokers (open symbols) and 4 smokers (solid symbols).

a higher urinary chemiluminescence than non-smokers and the results from bladder cancer patients are higher still with the highest of all results in the cancer patients who also smoked. These results confirm the findings of Schlegel *et al.* (1969) and the considerable degree of overlap found by the latter group has also been found here. The results reported here, however, show statistically significant differences between the groups in contrast to the results of Schlegel's group. The falls in urinary chemiluminescence following oral administration of ascorbic acid (Table IV and Figs. 10 and 11) were very striking. We have confirmed the findings of Schlegel *et al.* (1969) firstly that the fall in chemiluminescence is statistically significant and secondly that

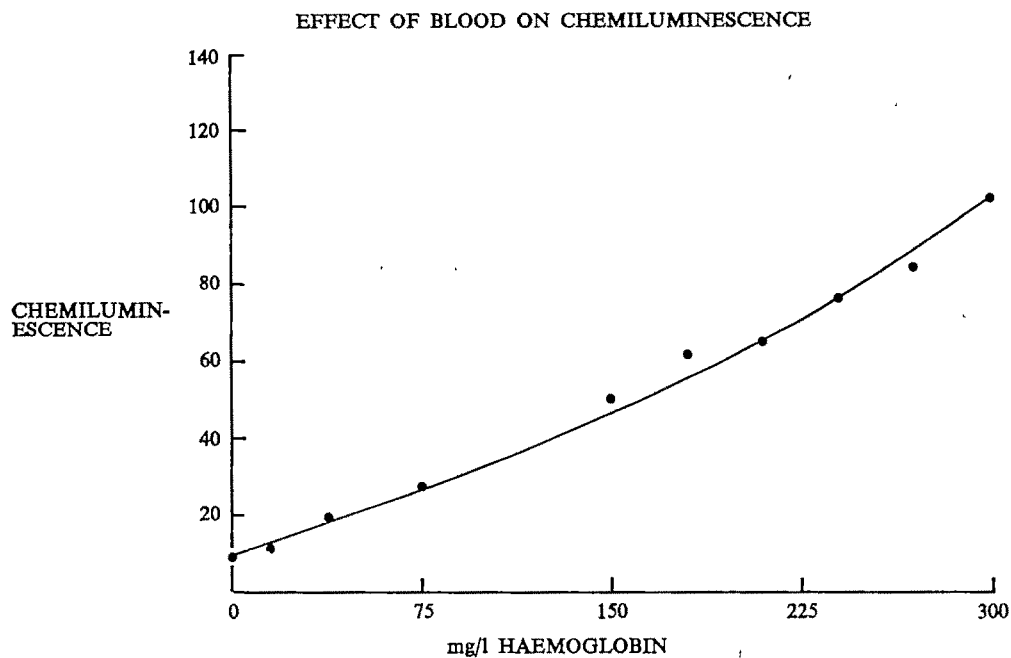


Fig. 7. Effect of increasing concentrations of whole blood in water upon observed chemiluminescence.

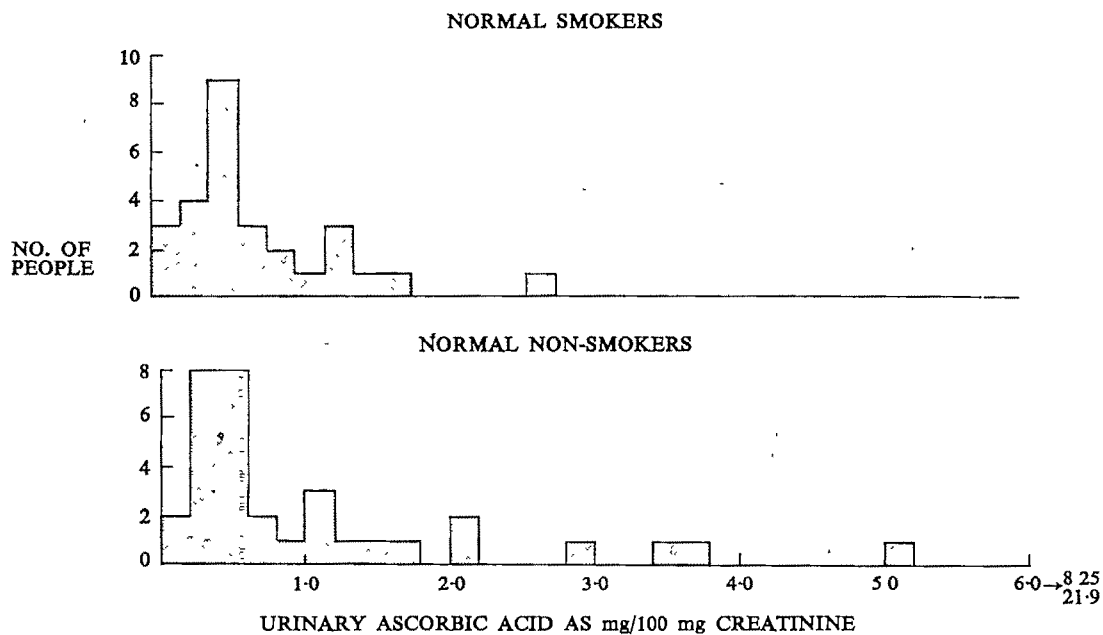


Fig. 8. Distribution of urinary ascorbic acid levels on urine samples from 38 normal non-smokers and 30 normal smokers.

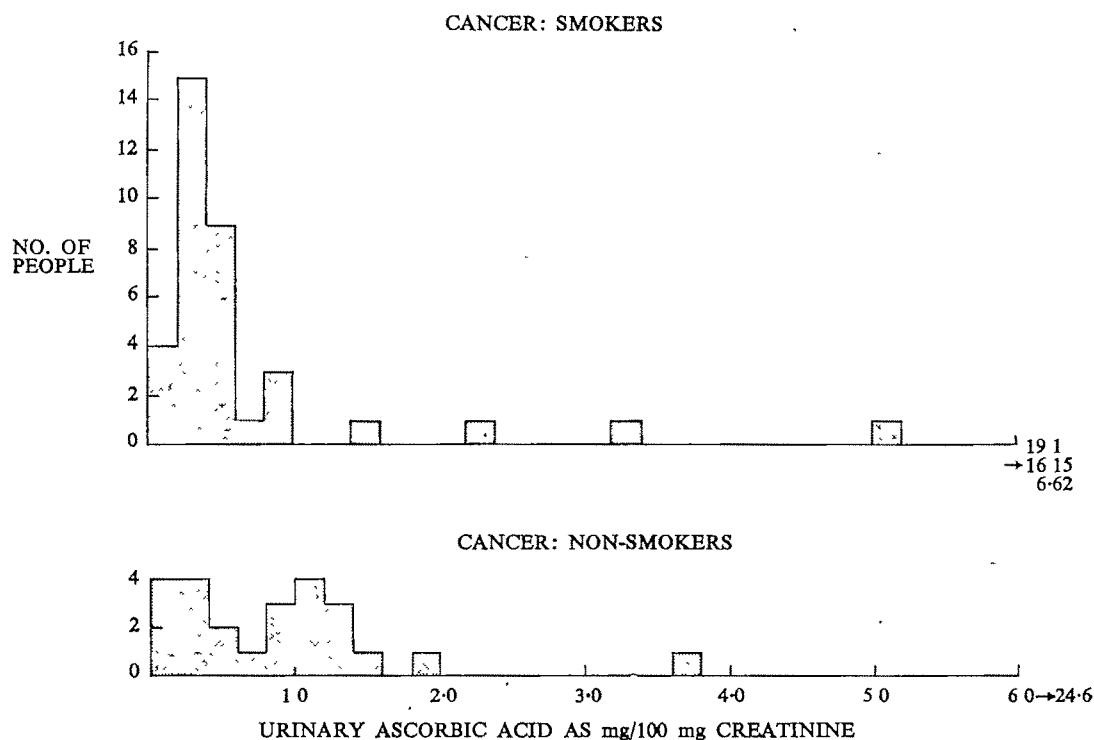


Fig. 9. Distribution of urinary ascorbic acid levels on urine samples from 75 patients with bladder cancer, 49 of whom were smokers and the remaining 26 non-smokers.

Table I

Chemiluminescence and Ascorbic Acid (corrected to Constant Creatinine) of Urine Samples of Normal Subjects and Patients with Bladder Cancer

	Chemiluminescence				Ascorbic acid mg/100 mg creatinine	S.E.M.
	Number	Mean	Range	S.E.M.		
<i>Normal Subjects</i>						
Non-smokers	28	40.9	16-108	0.32	0.68*	0.17
Smokers	27	51.3	11-178	0.45	0.62*	0.14
<i>Bladder Cancer</i>						
Non-smokers	22	54.7	23-122	0.41	0.71*	0.18
Smokers	37	58.8	17-274	0.27	0.48*	0.08

In order to calculate the mean and S.E.M. of the chemiluminescence for each group, the results are first put into the log mode which transforms the data into a normal distribution. For tests of statistical significance of chemiluminescence see Table III.

* No significant difference.

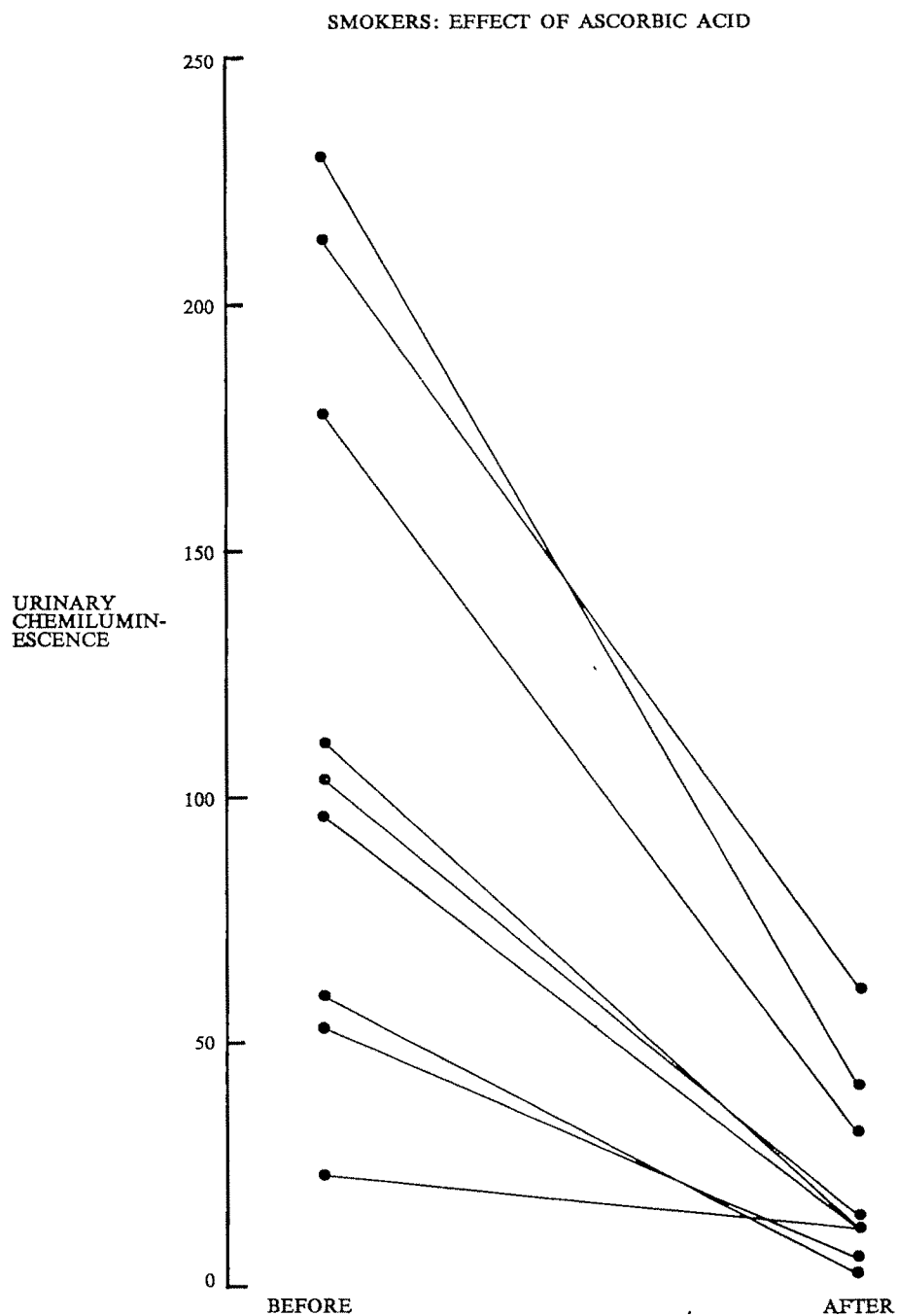


Fig. 10. Effect of oral administration of ascorbic acid upon urinary chemiluminescence per 100 milligrams creatinine of 9 normal smokers.

following ascorbic acid the urinary chemiluminescence was statistically greater amongst the smokers than amongst the non-smokers.

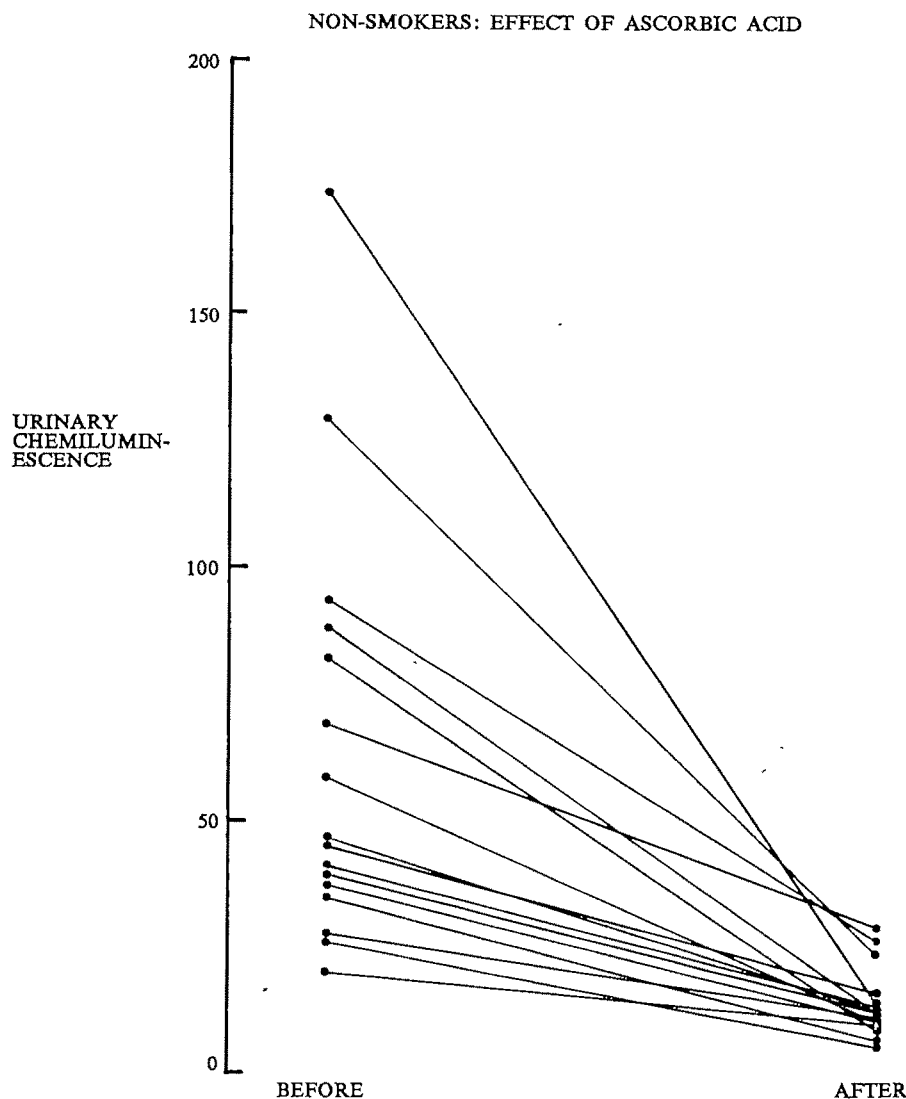


Fig. 11. Effect of oral administration of ascorbic acid upon urinary chemiluminescence per 100 milligrams creatinine from 16 normal non-smokers.

Conclusions

Although a link has been demonstrated between smoking and bladder cancer, the finding of raised urinary chemiluminescence amongst the smokers and the bladder cancer patients does not necessarily mean that chemiluminescence is a cause of bladder cancer. It merely indicates that there is a *prima facie* case for the further investigation of this hypothesis. Likewise, the finding that ascorbic acid lowers urinary chemiluminescence of normal subjects does not prove that administration of ascorbic acid could reduce the incidence of bladder cancer. It is stressed that

no case has been made out for the routine administration of ascorbic acid either to smokers or to patients with bladder cancer. There may be a case for a carefully controlled clinical trial of ascorbic acid, and it is hoped to embark upon this in the future.

Table II

Chemiluminescence (corrected to Constant Creatinine)
of Urine Samples of Smokers with Bladder Cancer
with and without Tumour Present

	Number	Mean	Range	S.E.M.
Tumour absent	24	49.7	17-124	0.34
Tumour present	13	80.2	31-274	0.54

Table III

"t" and "P" Values for Table I (Chemiluminescence only)

	Normal Smokers	Normal Non-smokers	Cancer Smokers	Cancer Non-smokers
Normal smokers	—	P = <0.01	P = <0.01	P = 0.05
Normal non-smokers	t = 15.6	—	t = 23.4	t = 38.7
Cancer smokers	t = 6.1	P = <0.01	—	t = 2.6
Cancer non-smokers	t = 2.0	P = <0.01	P = 0.05	—

Table IV

Urinary Chemiluminescence of Normal Subjects before and
after Administration of Ascorbic Acid

	No. of Subjects	Chemiluminescence/100 mg Creatinine		
		Mean	S.D.	S.E.M.
<i>Smokers</i>				
Before	9	96.6	2.10	0.70
After	9	15.4	2.56	0.85
<i>Non-smokers</i>				
Before	16	52.8	1.83	0.45
After	16	12.9	1.55	0.38

Each group is statistically distinct from all other groups.

An interesting and puzzling observation is the finding of higher urinary chemiluminescence amongst bladder cancer patients in whom tumour was actually present than amongst those with tumour absent (Table II). If it is true that chemiluminescence causes bladder cancer, this observation could mean that the likelihood of tumour recurrences can be assessed by measuring urinary chemiluminescence and the greater the latter the higher the risk of recurrence. Alternatively, however, it might be said that the tumour actually causes the chemiluminescence rather than vice versa and this point requires further investigation.

Summary

A relatively simple procedure for the measurement of urinary chemiluminescence is described and some of the variables affecting such measurements are examined.

Normal urinary chemiluminescence is due to a low molecular weight and freely dialysible compound. Addition of blood to urine causes chemiluminescence which is not dialysible.

Although there was very considerable overlap between the groups, it was found that urinary chemiluminescence was higher in normal smokers than in normal non-smokers and higher still in patients with bladder cancer. These results were statistically significant.

Considering only bladder cancer patients who were also tobacco smokers, the urinary chemiluminescence was higher when tumour was present than when tumour was absent.

Oral distribution of ascorbic acid reduced urinary chemiluminescence of both normal smokers and non-smokers.

There were no significant differences in urinary ascorbic acid levels between normal smokers and non-smokers, and patients with bladder cancer whether smokers or non-smokers.

We should like to express our thanks to Mrs H. Durbin for extensive technical help and also to Mrs N. Wallace for supplying urine samples and information from the Grove Health Centre, London, and also to the staff of these hospitals who assisted both by acting as normal subjects and by obtaining samples of urine from patients.

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Marjolin's Ulcer Complicating Suprapubic Cystostomy

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The development of malignant changes in sites of chronic irritation and ulceration and in burns scars has been well recognised since it was described in 1826 by Jean Nicholas Marjolin, though Hawkins (quoted by Sevitt, 1957) described the same condition in 1825. The neoplasms are nearly always squamous cell carcinomata, but basal cell carcinomata (Engler *et al.*, 1964) and sarcomata (Arons *et al.*, 1965) occasionally occur.

Marjolin's ulcers in relation to urinary fistulae appear to be uncommon, though Arons *et al.* (1965) describe 1 case complicating a urethral fistula of 25 years' standing in relation to a post-gonococcal stricture, and Anishin (1961) in Russia has reported a squamous cell carcinoma developing in relation to multiple perineal fistulae 17 years after wounding in the thigh and perineum with urethral damage. Perhaps surprisingly, Marjolin's ulcer in relation to a suprapubic cystostomy has not previously been described.



Case Report

Mr A. B. D.O.B. 26/1/78. He first presented in 1948 (aged 70) with 2 urethral strictures, one penile and the other in the bulbar urethra, which required dilatation with filiform bougies. In 1949 he developed a peri-urethral abscess; a suprapubic cystostomy was established. In 1969 a superficial skin infection occurred at the stoma but cleared with antibiotic therapy.

During these years his de Pezzer suprapubic catheter was changed with varying degrees of regularity. On 2 occasions dilatation of the stoma under general anaesthesia was required because of marked stenosis.

In 1971 a reddened area appeared around the stoma which was biopsied but showed no evidence of malignancy.

In 1972 at age 94, he was found to have a raised erythematous indurated area, surrounding two-thirds of the stomal circumference, which was ulcerated in one place (see Fig.). There was no associated inguinal lymph node enlargement. Cystostomy showed this abnormality to extend not more than half way down the cystostomy track and *not to involve the bladder* which contained clear urine and a number of calculi. A biopsy of the lesion showed it to be a well differentiated squamous cell carcinoma.

In view of his age and very frail state it was felt that surgery was contra-indicated and the primary site was therefore treated with radiotherapy.

He was given telecobalt therapy using wax build up. The total dose was 6,500 rads. given over an overall period of 57 days, using a pair of wedged fields, 6×6 cm at 90° .

In this case, as with many Marjolin's ulcers, the lesion was not a typical epithelioma and it is important to suspect the diagnosis in any lesion in a site of chronic trauma which does not heal with apparently adequate therapy, and where induration occurs beyond the visible boundaries of the lesion.

We wish to thank Mr H. F. Anderson, under whose care the patient was admitted, for permission to publish this case. We wish to thank Professor R. Raicher of the Urological Institute, Sofia, for translating the article published by N. S. Anishin in Russian.

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Three Cases of Cystic Seminal Vesicle Associated with Unilateral Renal Agenesis

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Cysts of the seminal vesicles are a rare condition; according to Sharma, Dorman and Dorman (1969) only 13 true unilateral cases have been reported up to 1969 and apparently only 4 were associated with ipsilateral renal agenesis. They may be asymptomatic and discovered by rectal examination or may give symptoms of bladder irritation, perineal or testicular pain, urinary obstruction or ejaculatory disturbances. The diagnosis is mainly based on vesiculography usually performed by retrograde injection of the vas deferens or eventually by direct puncture of the cyst itself. According to Heetderks and Delambre (1965) anatomical and microscopic confirmation of the origin of the tissue is required for the diagnosis to be acceptable. No true bilateral cases of seminal vesicle cysts associated with heterolateral renal agenesis have been found in the literature. The third patient herein reported is, to my knowledge, the first described case of bilateral cystic seminal vesicles.

Case Reports

Case 1. M. S. P., a 31-year-old, married fertile man was first seen on February 1970. He complained of pain in the right testicle, particularly at the moment of ejaculation. It had occurred during the very first time he had intercourse, when he was 17. The pain, that formerly used to be sudden and which quickly used to vanish after ejaculation, became progressively more intense and of long duration. Later on it began to spread to the perineum especially on the right side and he was experiencing an almost constant "painful sensation" in the same area, although less intense than it was during ejaculation. As intercourse became painful, the patient avoided it more and more frequently; ultimately, he thought that he was impotent.

The past history was absolutely unremarkable except for a surgical exploration in a military hospital. An I.V.P. had shown no right kidney and this was confirmed during that operation.

No abnormalities were found on physical examination except for a slightly tender right epididymis and an enlarged, firm nodule in the region of the right seminal vesicle. No urethral discharge was found. No fluid was obtained in prostatic massage. Blood and urinalysis were normal and the urine culture was negative. I.V.P. and radioisotope renogram confirmed the absence of the right kidney. Cystography on several occasions showed no changes of bladder outline and a barium enema was normal. Urethrocystoscopy revealed absence of the right ureteral meatus and of the right hemitrigone as well. Apart from a marked congestion of the verumontanum, where the ejaculatory orifices were not seen, the urethra was entirely normal.

Vesiculography was obtained after cannulation of the vas on both sides (Fig. 1). The left ampulla and seminal vesicle were normal but on the right side a cystic mass was clearly demonstrated in a rather high position. A dark brown fluid (25 cc) was aspirated; it showed few spermatozoa and a bacterial culture was negative.

After aspirating all the contrast medium used to visualise the vesicle, the vas was ligated and the incision closed. The whole symptomatology vanished soon after this investigation and it was decided not to operate. Several months elapsed before the recurrence of the symptomatology and, in the meantime, potency returned almost to normal.

On June 1970 the patient came in despair feeling much worse than on the first occasion. Another vesiculogram showed abnormalities identical to the previous ones, and complete relief was again obtained after drainage of the content of the vesicle.

A deferento-vesiculectomy was carried out through a midline suprapubic incision using the same technique reported in another paper (Linhares Furtado, 1971). The specimen was found to be multilocular (Figs. 2 and 3); there was no continuity with a normal ejaculatory duct or any other visible structure that could have represented it. The walls

of the cysts exhibited a very marked muscular hyperplasia and hyaline sclerosis; there was some vascular neoformation and nerve hyperplasia. No cellular inflammatory infiltrate was found.

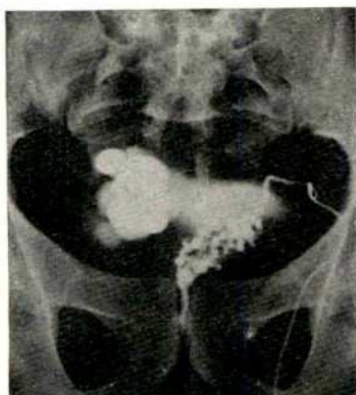


Fig. 1. Case 1. Bilateral vesiculography. Left ampulla, vesicle and ejaculatory duct entirely normal, allowing partial filling of the bladder. Right cystic vesicle is shown here completely filled up and its multiloculated appearance is evident.



Fig. 2. Case 1. The specimen after removal.



Fig. 3

Fig. 3. Case 1. The ampulla and vesicle opened to show their multiple cystic cavities.

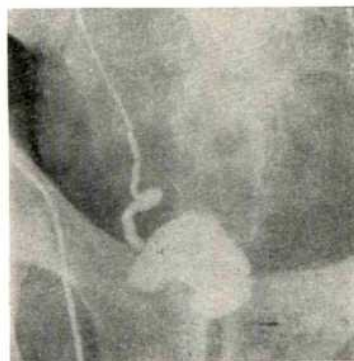


Fig. 4

Fig. 4. Case 2. Right cystic vesicle with no passage into the urethra.

The patient has had no further symptoms on the right side; his potency has greatly improved, but he has multiple and vague complaints quite different from the previous ones and apparently with no organic basis. He is afraid that he has cancer and is under psychiatric treatment.

Case 2. T. A. M., a 29-year-old, married man was referred for investigation of infertility. He complained of slight occasional dysuria and sometimes painful micturition. Physical examination revealed a small, non-tender, cystic nodule just above the prostate. He gave no past history relevant to a cause of infertility. The semen showed azoospermia. Routine blood and urinalysis were normal. An attempt at catheterising the ejaculatory ducts failed. Bilateral retrograde deferento-vesiculographies were carried out. On the right side the seminal vesicle was shown to be cystic (Fig. 4), apparently monolocular, without communication with the urethra; the left seminal vesicle and ejaculatory duct were entirely normal. An I.V.P. showed a perfectly normal left urinary kidney and ureter, but no right kidney was shown. The right hemitrigone and ureteral orifice were absent on endoscopy. The patient refused any treatment, but was relieved of dysuria and pain for a long time. No spermatozoa or bacteria were found in the content of the vesicles.

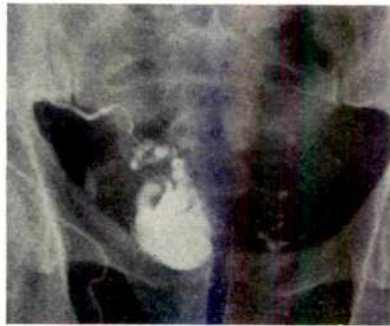


Fig. 5



Fig. 6

Fig. 5. Case 3. Cystic seminal vesicle on the right side. The fluid contrast medium did not pass into the urethra.

Fig. 6. Case 3. Left cystic seminal vesicle with free passage of contrast medium into the urethra and bladder. The ejaculatory duct seems to be dilated.

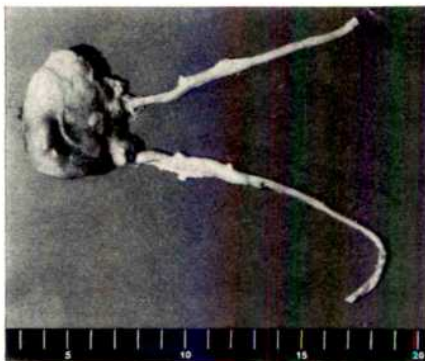


Fig. 7. Case 3. The seminal vesicles and vas deferens removed *en bloc*.

Case 3. J. E. dos S., a 41-year-old, married fertile man was first seen on March 1971. He had been suffering from dysuria, frequency, burning micturition and sometimes fever and chills with short periods of relief for the past 5 years. He was treated elsewhere with large amounts of various antibiotics for long periods, but his symptoms soon recurred every time antibiotics were withheld. For a time there was intense pyuria and purulent urethral discharge. More recently, perineal pain, exaggerated during defaecation was added to those symptoms. He also complained of a marked degree of sexual impotence and painful ejaculation which appeared at the same time as the other symptoms. There was no history of venereal disease.

Physical examination revealed some right supra-pubic tenderness and rectal palpation demonstrated a right-sided mass of about 4 cm in diameter, just above the prostate which felt normal. The mass was cystic in consistency, fixed and painful. After trying to compress it, no ureteral discharge was obtained. An I.V.P. and a radioisotope scanning showed absence of the left kidney. On endoscopy no left ureteral meatus and hemitrigone were seen. The absence of the left kidney and ureter was later confirmed during operation. The right kidney looked normal. A barium enema showed an anterior extrinsic compression of the rectum. Deferento-vesiculography (Figs. 5 and 6) showed abnormal seminal vesicles, the right one being spherical, bigger and with an ill-defined outline. It did not

communicate with the urethra. The left vesicle, although abnormal, had free drainage into the urethra. Bilateral *en bloc* seminal vesiculectomy (Fig. 7) was performed, a very marked inflammatory reaction being found mainly on the right side. The fluid was sterile and no spermatozoa were found in the right vesicle.

The pathological findings were very similar to those of the first case, except for the marked inflammatory reaction in the walls of the cysts. Recovery was satisfactory and all symptoms disappeared with the exception of his potency which was little improved.

Discussion

Apart from completely asymptomatic cases in which a cystic seminal vesicle is found by rectal palpation, the main symptoms associated with these cysts were present in these cases. The ipsilateral renal, ureteral and hemitrigonal agenesis found in the first 2 cases reported here is in agreement with what has been described by others (Kimchi and Wiesenfeld, 1963; Heetderks and Delambre, 1965; Reddy and Winter, 1972) and to the theoretical embryologic explanation for these associated abnormalities. The past history and the findings of the first 2 cases provide unquestionable evidence of their congenital origin.

The findings in the third case are rather more difficult to understand. The radiographic and pathological findings are consistent with the diagnosis of bilateral cystic vesicles and the accompanying agenesis clearly points to a congenital origin, at least on the left side.

However, there was free communication of the left vesicle to the urethra, a fact which does not fully agree with the possible theoretical explanation of the origin of these cysts, whether it be congenital or acquired. This fact casts some doubt on the view that this unquestionably abnormal seminal vesicle is a cystic one. If this is true, then the case might be considered one of unilateral cystic seminal vesicle associated with heterolateral urinary agenesis. No such case has been found in the current literature.

Another explanation could well be that cystic changes had occurred in the right vesicle during the past 5 years as a consequence of inflammatory obstruction of the ejaculatory duct and that the left vesicle is a peculiar case of a cystic vesicle of congenital origin, in which the ejaculatory duct remained patent. But one must stress the fact that the urethral discharge appeared well after the main complaints of the patient, suggesting the emptying of a seminal vesicle abscess into the urethra, rather than an abscess secondary to an ascending and obstructive duct infection.

This reasoning leads to the conclusion that this is a case of bilateral congenital cystic vesicles, associated with unilateral renal agenesis. This interpretation is not contrary to the embryological hypothesis, since cystic changes of the vesicle may co-exist with normal urinary tracts (Heller and Whitesel, 1963).

Two peculiar facts of these cases must be mentioned—the multilocular structure of the cystic vesicles of Cases 1 and 3 and the absence of spermatozoa in the fluid of 2 cystic vesicles. Thus, unlike what others (Hart, 1966) seem to suggest, the absence of spermatozoa does not exclude the diagnosis of cyst of the seminal vesicle. The return of sexual potency in the first case is also a remarkable fact which must be correlated to the relief of pain during ejaculation.

In the treatment of these lesions the suprapubic approach is easy, allows a perfect anatomical identification and removal of these vesicles while the bladder remains intact. Transurethral resection (Reddy and Winter, 1972) for those or similar cystic vesicles, which do not bulge into the bladder, or which have been repeatedly infected, does not seem advisable.

Summary

Three cases of cystic seminal vesicles associated with unilateral agenesis of kidney, ureter and trigone are reported.

In 2 of them, the cystic vesicle was unilateral with ipsilateral urinary agenesis.

The third patient had bilateral cystic vesicles and agenesis of the left kidney, ureter and trigone.

Several peculiar features of these cases are discussed. No other reported case of bilateral cystic seminal vesicles were found in the current urological literature.

A suprapubic surgical approach was preferred for removal of these vesicles.

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Agenesis of the Kidney Associated with Congenital Malformation of the Seminal Vesicle

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Renal agenesis is commonly accompanied by anomalies of the lower genito-urinary tract (Pasquier and Womack, 1953; Goldstein and Heller, 1956; Allansmith, 1958; Farr, 1960; Kimchi and Wiesenfeld, 1963; Schnitzer, 1965; Gordon and Kessler, 1972). According to Campbell (1963), failure or arrest of development of the Wolffian duct will cause agenesis of the isolateral primitive nucleus from which the corresponding urinary tract forms, with a resulting dysgenesis or absence of the isolateral urogenital apparatus. Reconstructive studies of the developmental anatomy of the human embryo have shown that when the pronephros and mesonephros develop normally, agenesis of the kidney and ureter can be accounted for by an anomaly in the next stage of development: the metanephrogenic mass fails to differentiate and form a kidney unless the primordial ureteric diverticulum grows into it. Incomplete absorption of the proximal end of the Wolffian duct, leaving the ureteral opening attached to it at the seminal vesicle site, would result in a persistent communication between the ureter and the vas at the site of the seminal vesicle (Allansmith, 1958).

Two such cases are herewith presented. In the first case there was agenesis of the left kidney, with an isolateral seminal vesicle cyst, and in the second case there was an ectopic ureter opening into a seminal vesicle cyst associated with isolateral renal agenesis.

Case Reports

Case 1. N. M., a 40-year-old male patient was admitted to our department because of dysuria, frequency and severe pain on ejaculation. The disorder had started 3 months before when he first noticed a discharge from the urethra. He had been given antibiotics with no effect.

On admission, the patient was in good general condition. Rectal examination revealed a cystic swelling palpable on the left side above the prostatic gland. The swelling was slightly tender. Laboratory results were normal except for a leucocytosis of 9,000 cells/mm³. Intravenous pyelography showed agenesis of the left kidney and compensatory hypertrophy of the right kidney (Fig. 1, A), as well as a filling defect on the left side of the bladder (Fig. 1, B). The agenesis of the left kidney was confirmed by angiography. Cystoscopy revealed the absence of the left side of the trigone. This area was raised and bulged into the bladder due to a space-occupying lesion behind it. A vesiculogram performed through the left vas deferens revealed a huge seminal vesicle cyst (Fig. 2).

Operation was performed through a suprapubic incision. The seminal vesicle cyst was exposed and excised without opening the urinary bladder. The postoperative course was complicated by the development of left orchitis with a high fever which subsided gradually in response to antibiotic therapy. The patient left the hospital well 3 weeks after operation.

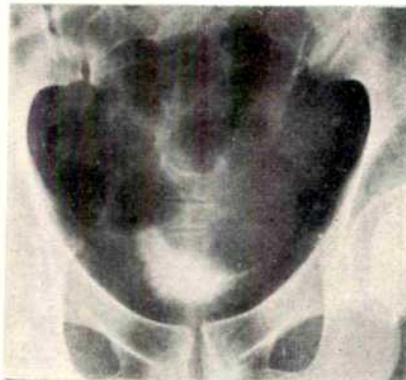
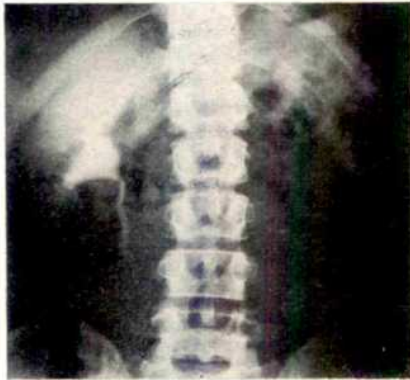


Fig. 1. A. Case 1. I.V. urography, showing agenesis of the left kidney. Note compensatory hypertrophy of the right kidney. B. Case 1. I.V. urography, showing an almost round filling defect on the left side of the bladder after voiding.



Fig. 2. Case 1. Vesiculography, with the dye injected via the left vas deferens. Note tortuosity of the vas deferens before entrance into the huge vesicle seminal cyst.

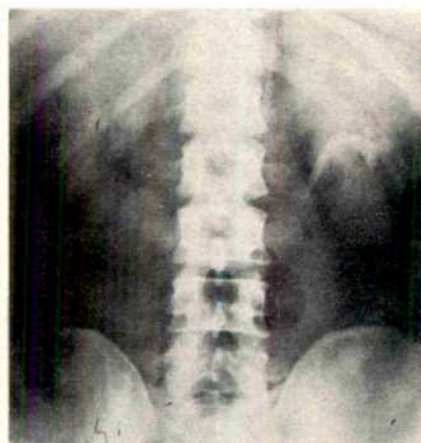


Fig. 3. Case 2. I.V. urography, showing agenesis of the right kidney with compensatory hypertrophy of the left kidney.

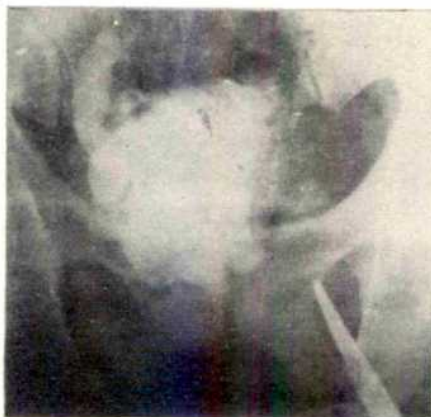


Fig. 4. Case 2. Intraoperative-puncture seminal vesiculography: note reflux into right ectopic blind ureter.

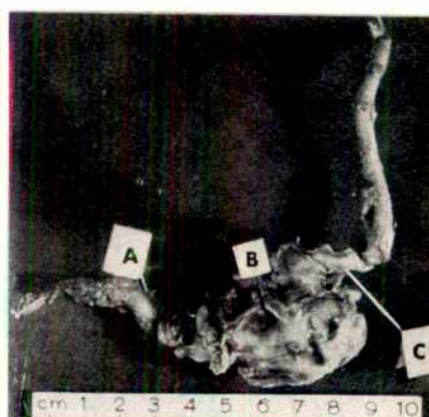


Fig. 5. Case 2. Macroscopic view of the surgical specimen (after formalin fixation). A, Ectopic ureter. B, Seminal vesicle. C, Vas deferens.

Case 2. Y. L., a 36-year-old male was admitted to our department with a complaint of dysuria and pain in the anal region which was worse on ejaculation. The disorder had begun 6 years before with severe dysuria which had necessitated his being admitted to a urological department elsewhere. He had undergone a laparotomy and had been told that he had a solitary kidney on the left side. He was also told that during the operation they had found a cyst of the right seminal vesicle which had been aspirated (the medical report of this hospitalisation could not be retrieved by us). After the operation he felt well for only a few months, after which his complaints reappeared.

On his admission he was well. Rectal examination revealed a tender swelling above the right lobe of the prostate. Laboratory examinations showed no abnormalities. An I.V.P. showed absence of the right kidney and compensatory hypertrophy of the left kidney (Fig. 3). This was confirmed by aortography. Cystoscopy showed the absence of the right half of the trigone. In its place there was a swelling caused by an extravesical space-occupying lesion.

A vesiculography through the right vas deferens was unsuccessful. After the bladder had been opened, the contrast medium was injected directly into the right seminal vesicle. A cystic seminal vesicle with reflux into a ureteral stump was demonstrated (Fig. 4). We proceeded to excise the seminal vesicle cyst and its ectopic ureter (Fig. 5).

The postoperative course was uneventful and the patient was discharged symptom-free.

Comment

Anomalies of the seminal vesicle are rare. An autopsy study of 10,919 boys showed only 6 such cases (Campbell, 1963). Congenital agenesis of the kidney is, on the other hand, more common. According to various authors cited by Campbell (1963), its incidence ranges between 1 : 552 to 1 : 1,286.

In the series of 61 males with ureteral ectopia collected by Thom (Campbell, 1963), the orifice was found in the seminal vesicle in 17.

The parallel occurrence of 2 separate events—i.e. (a) the failure of the ureteric diverticulum to grow into the metanephros, plus (b) incomplete absorption of the proximal end of the Wolffian duct—may well explain the mechanism involved in the congenital malformations found in both our cases. A redundant ectopic ureter opening into a seminal vesicle cyst may well be one variant of a whole spectrum of congenital anomalies which can take place should there be a faulty embryological shifting of position and displacement of organs. Thus, a functioning kidney may be found, a hypoplastic, non-functioning kidney may be discovered or agenesis of the kidney may occur. The ureter may be found in its entirety, only part of it may exist opening into a seminal vesicle or it may be completely absent.

Summary

Two cases with agenesis of the kidney and an isolateral seminal cyst have been described.

In 1 case there was also an ectopic opening of a blind, isolateral ureter.

Brief comment is made on the embryological basis for these anomalies.

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Bilateral Caverno-saphenous Shunt for Priapism: 4 Case Reports

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Priapism is defined as a prolonged, painful and persistent erection of the penis, without sexual desire. The therapeutic procedures for the treatment of priapism are of a great variety and the results are contradictory.

Until recently, before the physio-pathological mechanism was better understood mostly conservative procedures were used, which resulted in the establishment of irreversible intra-corporal lesions.

After the theories of Hinman (1960), based on the anatomical studies of Conti (1953), its management was approached by a more rational way and now a more active approach is adopted in which these patients are treated as surgical emergencies (Howe *et al.*, 1969).

Grayhack *et al.* (1964) published a new surgical technique which consisted in the by-pass of the stagnated blood in the corpora cavernosum through a corpus-saphenous shunt. Since then, the experiences have increased in various specialised centres, and the results have been, generally speaking, satisfactory.

We report our experience with 4 cases of idiopathic priapism treated by bilateral sapheno-cavernous anastomosis.

Case Summaries

Case 1. J. I. L., 32-year-old, single, Negro, reg. 80320, admitted on 23rd September 1970 with an erection that had not subsided since it had been initiated spontaneously 3 days previously. The patient had no past history of priapism. He had tried, on his own and without results, ice packs, anti-spasmodics and analgesics. He was first examined in the Emergency Room where narcotics and spinal anaesthesia were used, also without satisfactory results. General physical conditions were good. Local examination revealed erection of the penis, forming an acute angle with the pubic symphysis, corpora cavernosa engorged and distended, and the corpus spongiosum of a normal consistency. Chest and dorso-lumbar X-rays were normal. BUN 48 mg %, blood sugar 90 mg %, creatinine 1.2 mg %. Urinalysis and CBC were within normal limits. The patient was taken to the O.R., and a spinal anaesthesia was again performed, without any change in the priapism. After the preparation of the operative field, a cutaneous incision of approximately 10 cm long was made in the lateral-medial and superior aspect of the left thigh. The saphenous vein was identified and dissected free from its tributaries for a length of about 8 cm, ligated and incised distally. The proximal venous segment was then brought through a subcutaneous tunnel to the base of the penis, where a cutaneous incision was made and extended to the Buck's fascia. An elliptical incision was made in the corpus cavernosum and through it irrigation was performed with heparinised solution. The saphenous vein was then anastomosed to the corpus cavernosum with 5/0 black silk continuous suture. Suction helped to clear the operative field. At the end of the procedure, the anastomosed venous segment was engorged and distended, and the penis was in a semi-flaccid state. An identical procedure was immediately performed on the opposite side, at the end of which the penis was completely flaccid (Fig. 1). A urethral catheter was left indwelling for 48 hours. Systemic heparin was not used postoperatively. His postoperative course was uneventful. The patient was discharged 1 week after surgery. Sexual potency completely recovered.

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Case 2. I. V. G., 30-year-old, single, mulatto, reg. 111581, admitted on 25th December 1970 with priapism for 9 days. Past history unremarkable. The erection was confined to the corpus cavernosum as the corpus spongiosum was flaccid. In another local hospital conservative measures, analgesics, anti-spasmodics, narcotics, systemic heparin and spinal anaesthesia, had been carried out, without favourable response. Laboratory and radiographic data were normal. Bilateral corpus-saphenous anastomosis was immediately performed as previously described. Again we did not use heparin systemically. Patient discharged from hospital 1 week after operation. Sexual potency only partial and insufficient for normal intercourse.

Case 3. I. S., 32-year-old, married, white, reg. 167183, admitted on 8th July 1971 with priapism for 2 days. He had been examined in another hospital on the day prior to admission, where aspiration of the corpus cavernosum under spinal anaesthesia had been performed without satisfactory response. The patient had had a similar episode 1 year previously, which subsided spontaneously after 2 days. Physical general examination was unremarkable except for the presence of penile erection. Corpora cavernosa engorged and distended. Minimal distention of the corpus spongiosum. Laboratory and radiographic data showed no abnormality. Bilateral sapheno-cavernous shunt was performed. Heparin was not used systemically. On the first postoperative day he developed left orchitis which was treated with anaesthetic block of the spermatic cord. Patient discharged 2 weeks after operation. Sexual potency completely recovered.

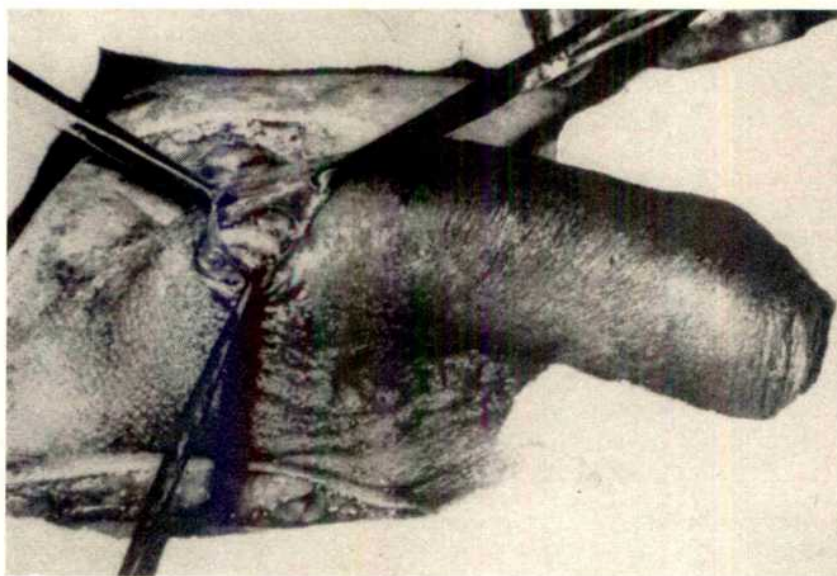


Fig. 1. Anastomosis caverno-saphenous finished. Penis completely flaccid.

Case 4. Z. G. V., 32-year-old, single, white, reg. 296495, admitted on 15th July 1972 with priapism for 7 days. Episode of acute urinary retention 24 hours prior to admission. In another hospital conservative measures including spinal anaesthesia had been carried out without positive response. His physical general condition was fair. The corpus cavernosum and the corpus spongiosum were both involved. Radiographic studies and blood chemistry within normal limits. The blood count showed moderate anaemia. Bilateral corpus-saphenous shunt was immediately performed. His postoperative course was complicated by an abscess on the right thigh which was incised and drained. Patient discharged 3 weeks after surgery. Sexual potency did not recover.

Comment

It is widely accepted that the idiopathic cases must be treated as surgical emergencies using one of the blood by-pass techniques (Grayhack *et al.*, 1964 and Quackels, 1964). Analysing our 4 cases, we observed that immediate flaccidity became complete only after the bilateral anastomosis. It seemed to us that the channels through the septum pectiniforme were insufficient—at least in the beginning—to produce satisfactory drainage from one side. Another advantage of the bilateral anastomosis would be less likelihood of bilateral thrombosis in the postoperative phase.

The best results could probably be obtained by the use of the bilateral sapheno-cavernous shunt initially, performing later on, if needed, the cavernous-spongy anastomosis. We also noted that in Cases 2 and 4, with priapism for 1 week or longer, the patients became sexually impotent. This observation agrees with the general feeling that the occurrence of sexual impotence, no matter what type of treatment used, is directly proportional to the duration of the disease (Medeiros, 1972). We believe, like the majority, that the surgical treatment by venous by-pass, performed in the first 48 hours, will cure the priapism and will diminish the possibility of further sexual impotence.

Summary

The authors present 4 cases of idiopathic priapism treated with bilateral sapheno-cavernous shunt, and discuss the immediate and late results obtained by this technique. It was observed that immediate total penile flaccidity had occurred only after completion of the bilateral shunt. Sexual impotence occurred in 2 cases on whom the surgery was carried out 1 week after the illness, confirming the general feeling that the occurrence of future sexual impotence is directly proportional to the duration of the disease.

They believe that best results would be obtained with the use of the bilateral corpus-saphenous shunt, initially, performing later on, if necessary, a cavernous-spongy anastomosis.

The necessity to treat these cases as surgical emergencies is emphasised.

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Lymphography in Patients with Testicular Tumours

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Lymphography has been used in clinical practice for more than 15 years. The method, initially described by Kinmonth (1952), Kinmonth, Harper and Taylor (1955a) and Kinmonth, Taylor and Harper (1955b) has with minor technical modifications been used ever since. The main application is to evaluate the presence of disease in the retroperitoneal lymph nodes. Good results have been achieved in the investigation of lymphoma and lymphoedema. Its value concerning presence of lymph node metastases is more questionable. Several authors have presented their experience with lymphography in cases of malignant testicular tumours (Seitzman and Halaby, 1964; Cook *et al.*, 1965; Körner and Hilweg, 1968; Burgener and Fuchs, 1969; Langhammer, 1969; Wallace, 1969; Fuchs, 1970; Wallace and Jing, 1970; Hintzen *et al.*, 1971; Maier and Schamber, 1972). Three of them (Seitzman and Halaby, 1964; Cook *et al.*, 1965; Wallace and Jing, 1970) have reported a relatively high percentage of false negative cases.

The main criteria of a pathological lymphography in cases of metastases are (Fischer, 1968; Wallace and Jackson, 1968; Hintzen *et al.*, 1971; Maier and Schamber, 1972): (1) Marginal filling defects, exceeding 5 mm in diameter. (2) Lymph vessel deviation. (3) Blockage of lymph flow. (4) Lack of filling of groups of lymph nodes.

This paper will present our experience with the criteria and their value in the diagnosis of metastases of testicular tumours, by comparing findings at lymphography and retroperitoneal lymph node dissection.

Patients

During the 12-year period 1960-71, 86 patients with testicular tumours have been treated at the Department of Urology, University Hospital of Lund, Sweden. After orchidectomy 44 of these patients were examined by lymphography, in 28 cases combined with cavography and urography. 16 patients had seminomas and 2 had reticulum cell sarcomas. These 18 patients were treated with irradiation of the retroperitoneal lymph nodes, and no operative confirmation of metastases was made.

26 patients had malignant teratomas. Of these, 22 patients were operated upon with retroperitoneal lymph node dissection. The remaining 4 patients had extensive retroperitoneal lymph node metastases or lung metastases, and no operation was done.

The interpretation of the lymphographies presented in this paper represents a re-evaluation of the examinations without knowledge of the finding at operation.

Technique of Lymphography

After careful washing of the feet, 1-2 cc of 1% methylene blue in 0.5% xylocain^(R) is injected intra-/subcutaneously in the web between the first and second toe. In some cases one or more interdigital webs are injected. A few minutes later, a short transverse incision is made under local anaesthesia on the dorsum of the foot at the level of the navicular bone. A blue-stained lymph vessel is carefully dissected out, and a 27 or 30 gauge needle on a catheter is introduced into the lumen of the lymph vessel, and then tied with a silk ligature. On each side 6-8 cc

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of Lipiodol Ultrafluide^(R) is injected with an automatic injector (Clementz and Olin, 1961) at the rate of 4 cc/hour. At the end of the injection AP and right and left oblique films are taken of the pelvis and the para-aortic regions. After 24 hours, the patient is again examined with films taken in the same projections.

In 28 cases, cavography, followed by urography, was made after the 24 hours' examination had been made.

Results

Of the 44 lymphograms, 4 were successful on 1 side only. In these cases the tumour was a seminoma. In 1 case with malignant teratoma, there was a lymph-cyst in the left groin, secondary to a lymph node biopsy made at the same time as left-sided orchidectomy. No contrast medium passed further up on the left side. The remaining 39 lymphograms were technically successful on both sides and allowed proper interpretation. In all the successful cases, except 1, collaterals were seen across the midline from right-sided lymph vessels to left-sided para-aortic lymph nodes.

Table

Findings at Lymphography

Changes	Positive at Operation (12 Patients)	Negative at Operation (10 Patients)
Marginal filling defects	3	1
Uncharacteristic filling defects	3	4
Deviation of lymph vessels	7	0
Lymph vessel obstruction	2	0
Empty space	2	0
Normal	1	5

The table indicates that in most cases with pathological lymphography there is a combination of criteria of malignant involvement.

Good correlation between lymphography and findings at operation was found in 19 cases; 10 cases were found to have metastases and 9 were normal. Lymphography gave a false positive in 1 case and a false negative in 2 (Table).

In 12 cases with operatively and histologically proven metastases, 3 had filling defects of malignant type (Fig. 1, A). Seven cases had lymph vessel deviation as a sign of metastases (Fig. 2), and in 3 of these, there was deviation of the cisterna chyli from the midline (Fig. 3). This was the only sign of a retroperitoneal mass in 1 patient. In the other 2, there was a slight deviation of other lymph vessels in the area. In 2 patients lymph vessel blockage was seen, in both cases combined with deviation, as a sign of metastatic disease (Fig. 2).

In 2 cases there was a lack of filling of a group of lymph nodes in the para-aortic lymph node chain on the left side, at the level of L2-3 (Fig. 4). Corresponding to this non-filled group there was a lateral deviation of the left ureter at urography.

Of the 2 cases with false negative lymphography, 1 was completely normal. The second case was the one with a lymph cyst in the left groin, after lymph node biopsy. At operation widespread para-aortic lymph node metastases were found on the left side. This was the only case where no collaterals were seen from the right to the left.

One case with false positive lymphography had a marginal filling defect of malignant type in 1 lymph node.

Uncharacteristic central filling defects (Fig. 3, B) were found in 7 patients.

In no case was there lymphographic or clinical evidence of supraclavicular metastases.

In the patients undergoing operative treatment, cavography and urography gave additional information to lymphography in 3 cases (Figs. 1, B and 4).

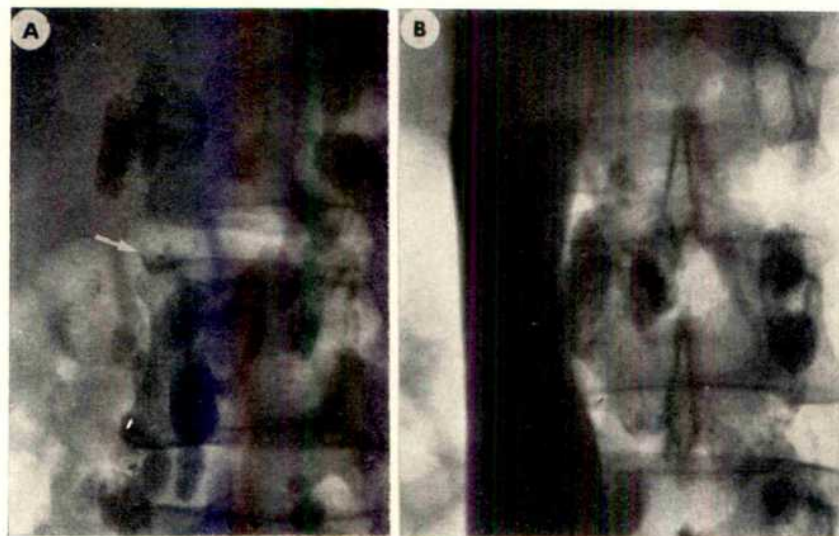


Fig. 1. I. I. 31-year-old male with right-sided malignant testicular teratoma. A, At the level of the intervertebral disc L2-3 a right-sided lymph node is seen with a large marginal filling defect in the cranial part. Only a small part of the lymph node is filled with contrast (arrow). B, Cavography: Indentation in the left part of inferior vena cava below the left renal vein, indicating a larger extension of metastases than is seen at lymphography. At operation there was a group of malignant nodes between the caval vein and the aorta below the level of the left renal vein.

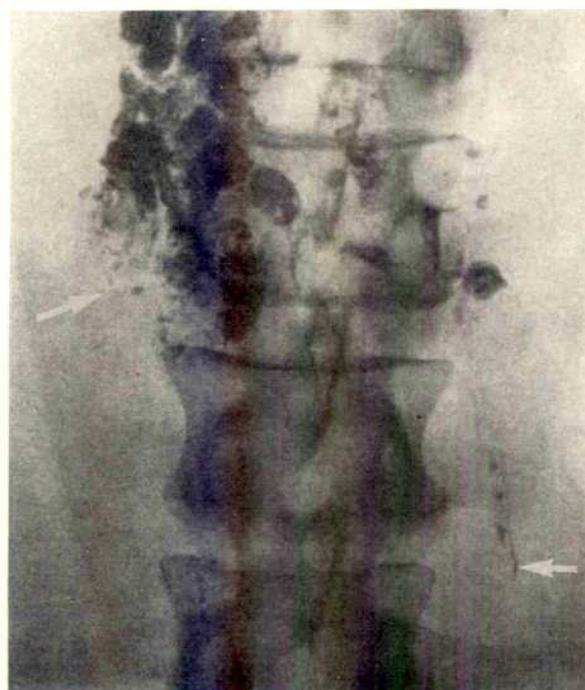


Fig. 2. L. N. 29-year-old male with right-sided malignant teratoma. At the 24-hour pictures are seen deviated and obstructed lymph vessels (arrows). No lymph node dissection was performed because of widespread retroperitoneal metastases.

Discussion

For interpretation of lymphography concerning lymph node metastases, it is of utmost importance to know the primary lymph drainage of the involved organ. The lymph drainage of the testes accompanies the spermatic artery and vein to lumbar lymph nodes, usually situated at the renal vein (Rouviere, 1932). These lymph nodes may have a wide variation and can be situated from T11-L4 on the ipsilateral side (Busch, Sayegh and Chenault, 1965). As in other reports (Busch and Sayegh, 1963; Seitzman and Halaby, 1964; Busch *et al.*, 1965; Körner and Hilweg, 1968; Burgener and Fuchs, 1969; Wallace, 1969; Maier and Schamber, 1972), a constant crossing over from the right to the left was seen in our material. In only 1 case were there no crossing vessels

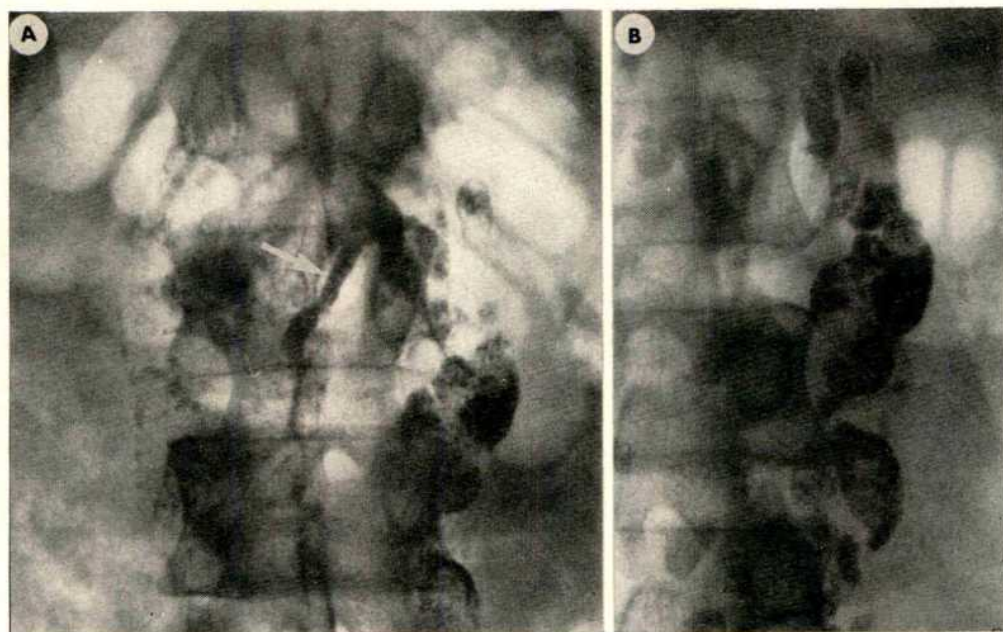


Fig. 3. B. H. 27-year-old male with right-sided malignant teratoma. A, Cisterna chyli is deviated to the left (arrow). B, Left-sided, rounded lymph nodes with uncharacteristic filling defects. At operation right-sided metastatic lymph nodes at the level of L1-2 were found and microscopic evaluation showed no lymphography contrast medium was seen in these nodes. The left-sided lymph nodes were enlarged and hard. Histology revealed fibrolipomatosis.

and no opacified left-sided lymph nodes because of extensive left-sided para-aortic lymph node metastases. If lymphography for some reason is unsuccessful on 1 side, especially on the left, the lack of filling of crossing collaterals is an observandum, which should arouse suspicion of metastatic disease on that side.

At lymphography contrast filling of supraclavicular lymph nodes is often seen. The same finding has been noticed at testicular lymphography and therefore it was claimed that "as regards metastasization from testicular tumours... supraclavicular lymph nodes probably are as important as the lumbar nodes on both sides" (Wahlqvist, Hultén and Rosencrantz, 1966). However, in none of our cases was there any lymphographical or clinical evidence of supraclavicular metastases.

Marginal filling defects are considered to be the main criteria of metastases. In our material only 4 cases had typical filling defects (Fig. 1, A), and 1 of these proved to be false positive. Uncharacteristic central filling defects (Fig. 3, B) are common in the lumbar level, and they usually represent fibrolipomatosis. In our material they appeared in 4 non-metastatic cases and

in 3 cases with metastases, proven at operation and with histology not to represent metastases. Thus, filling defects in general are an unreliable sign, except when the filling defect is of typical marginal type with obstruction of the afferent vessels.

The normal lymph nodes are flat and elongated, but in case of disease they increase in volume and obtain a more spherical shape, especially in cases of metastases (Wiljasalo, 1965). An index has been calculated to prove the spherical form of the involved nodes. In none of our cases with marginal filling defects have we been able to use this index because the contrast-filled part of the nodes was too small to measure the whole lymph node diameter. Several cases with uncharacteristic central filling defects, proven to be due to fibrolipomatosis, had a rounded appearance (Fig. 3, B). We are thus doubtful of the general application of this index as an indication of metastases.

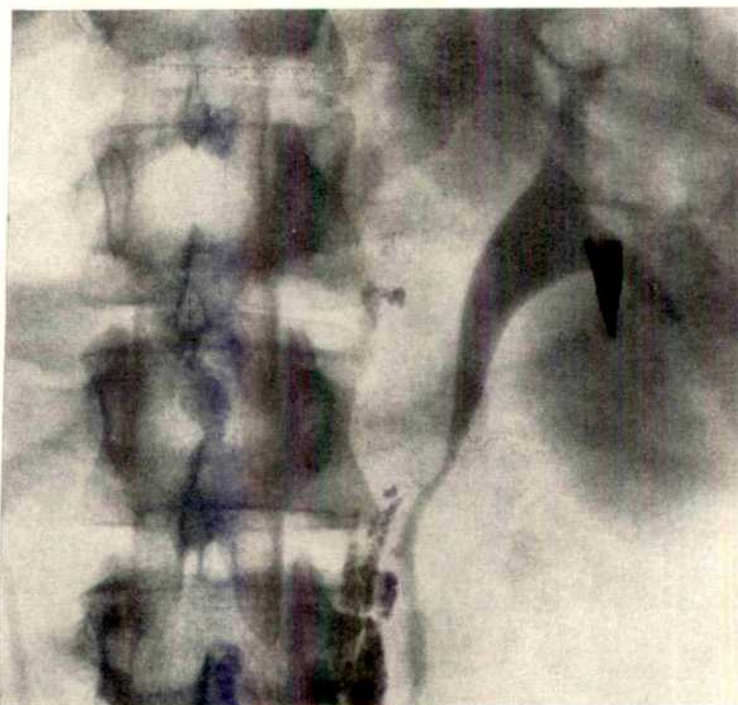


Fig. 4. B. S. 29-year-old male with left-sided malignant teratoma. At lymphography an empty space in the left para-aortic lymph node chain is seen at the level of L2. Corresponding to this empty space there is an indentation and slight deviation of the left ureter.

In our material lymph vessel obstruction and deviation (Fig. 2) proved to be the most reliable sign of metastatic disease. This could be expected since in most cases the diseased lymph nodes were totally replaced by tumour, with no contrast filling at lymphography.

Three cases had deviation of the cisterna chyli from its normal midline position as a sign of a retroperitoneal mass. Deviation has previously been described in malignant lymphogranulomatosis (Davidson, 1969), but we have not seen any report representing cases of lymph node metastases. It is, however, an inconstant sign, since the cistern is seen in only 30% of all lymphographies (Fuchs and Galeazzi, 1970). The same rate was found in our total material. The application of this sign is of importance in cases with testicular tumours, because the cistern is situated in the same area as the primary lymph nodes of the testis.

The lack of filling of a group or chain of lymph nodes has been considered to prove lymph node disease (Körner and Hilweg, 1968; Hintzen *et al.*, 1971; Maier and Schamber, 1972), but

other authors (Wallace, 1969; Fuchs, 1970) have given it small proving importance, because of the great variability of the lymph node anatomy.

In our material there were 2 cases with a non-filled group of lymph nodes in the left para-aortic lymph node chain at the level of L2-3 (Fig. 4). This *per se* did not prove the presence of metastases, but at urography, following cavography, a lateral deviation of the ureter at this level was found.

In addition to these 2 cases, cavography and urography gave additional information to lymphography in 1 more case, where the contrast-filled part of a malignant node was quite small (Fig. 1, A). At cavography an impression was seen which made the malignant node obvious (Fig. 1, B).

It has been claimed (Baum *et al.*, 1963; Hopf and Fuchs, 1970) that the combination of the 3 examinations increases the information gained in about 10%, which is also found by us.

To improve the detection of metastases, techniques for testicular lymphography have been described (Busch and Sayegh, 1963; Chiappa *et al.*, 1963; Busch *et al.*, 1965; Cook *et al.*, 1965; Chiappa *et al.*, 1966; Wahlqvist *et al.*, 1966; Kuisk *et al.*, 1970), which have given more information, and for complete evaluation of the retroperitoneal lymph system, a combination of foot and testicular lymphography is necessary (Chiappa *et al.*, 1966; Wahlqvist *et al.*, 1966; Wallace and Jing, 1970) as the primary testis lymph nodes "the testis lymph center" (Chiappa *et al.*, 1966) are inconstantly filled with contrast by pedal lymphography.

In our material, extra information might be expected from testicular lymphography in only 2 cases, namely the 2 with false negative lymphograms.

Of 22 cases, lymphography has given the correct diagnosis of lymph node metastases in 19. It would be only a slight improvement to demonstrate metastases in 1 or 2 more cases by performing testicular lymphography, as the findings at lymphography *per se* are not an indication for lymph node dissection. The examination is made to help the operator to find the metastatic lymph nodes at operation, but the primary testicular lymph nodes are always explored.

We are of the opinion that the combination of pedal lymphography, cavography and urography in the hands of an experienced radiologist gives good results in the diagnosis of lymph node metastases in cases of testicular tumours.

Conclusions

Filling defects are an unreliable sign of metastatic disease.

Obstruction and deviation of lymph vessels, including the cisterna chyli, is a valuable sign of disease.

In only 1-sided technically successful lymphography, the lack of filling of crossing vessels should make the radiologist suspect retroperitoneal metastases.

The combination of lymphography, cavography and urography gives increased information concerning the presence of retroperitoneal disease in about 10% compared to lymphography alone.

A normal lymphography is no guarantee of the absence of metastases, but an abnormal lymphography is of value to the clinician in order to help him find the diseased lymph nodes at operation.

Summary

The findings at lymphography and retroperitoneal lymph node dissection were compared in a retrospective study of 22 patients with malignant teratoma of the testes. The lymphographic criteria of lymph node metastases are assessed.

The deviation of lymph vessels, often in combination with obstruction, was the most reliable sign of metastases in our material. The lack of filling a group of lymph nodes was a sign of metastases only if cavography and/or urography were pathological in the same area; otherwise this was not a reliable sign.

Marginal filling defects were of minor importance in the diagnosis of lymph node metastases. Supported by a grant Nr K73-17X-521-10 from the Swedish Medical Research Council.

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Incision of the External Inguinal Ring in Acute Epididymitis

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Some patients with acute epididymitis respond unsatisfactorily to adequate conservative treatment. They tend to have a protracted course with considerable pain, progression of the local lesion and sometimes marked constitutional disturbances. The reasons why this should occur are not accounted for in the literature, but it has been recommended that tension in the epididymis should be relieved surgically by puncturing the epididymis with a large needle, the operation of epididymotomy (Macdonald, 1970). Occasionally epididymectomy or orchidectomy has been necessary (Campbell, 1928). The development of gangrene of the testis, due to a remarkable oedema of the cord with venous and arterial thrombosis has been reported by Gartman (1961) in 3 patients.

In this Unit the operation of epididymotomy through the usual scrotal incision, in these unresponsive cases, has frequently led to wound disruption, followed by the discharge of sloughing testicular tissue with consequent loss of the testis. Nevertheless, the operation did dramatically relieve the patient's pain and his constitutional symptoms. Because of this complication it was decided that epididymotomy should be performed through an inguino-scrotal incision, so that the skin incision would not overlie the inflammatory site. Using this approach to explore a testis during an episode of epididymitis, in a patient known to be subject to recurrent attacks, marked oedema and engorgement of the cord was noted. This extended up to the external inguinal ring and was relieved dramatically, during the short period of exploration, after incising the edge of the external inguinal ring, which appeared to act as an obstructive factor to venous return. Since this operation an inguino-scrotal incision has been used routinely when exploring an acute epididymitis, paying special attention to the state of the cord at the external inguinal ring. If the cord is oedematous and there appears to be venous engorgement, an adequate incision is made in the edge of the ring. No further cases of wound disruption or sloughing of the testis have occurred since adopting this policy.

Case Reports

Seven patients treated by this method illustrate this principle.

Patient 1. 12 hours prior to admission this 26-year-old patient wakened with pain in the left testis, which gradually became more severe. He had experienced a similar attack 1 year previously which had resolved spontaneously. There were no symptoms or signs of urinary tract infection or urethral discharge. On examination he was afebrile, the left epididymis was markedly enlarged and tender and the testis and cord appeared to be uninvolved. The patient was confined to bed, the scrotum was elevated and he was given analgesics and ampicillin 500 mg 6-hourly. During the next 36 hours he became mildly pyrexial, the pain increased, the overlying scrotal skin became red and oedematous, swelling of the epididymis became more marked, a secondary hydrocele developed and the cord itself became thickened and tender. At exploration the cord was found to be oedematous up to the inguinal ring, the epididymis was congested and swollen and the testis was tense and blue. There was no evidence of torsion. The external inguinal ring was incised with immediate improvement in the colour of the testis, and the oedema of the cord was noted to decrease. The tunica albuginea was incised and a testicular biopsy performed. This showed normal viable tubules and marked interstitial haemorrhage, consistent with early infarction. An epididymotomy

was performed. Postoperative recovery was rapid and uncomplicated. When seen 6 weeks later at follow-up clinic, the testis was noted to be small and considered to be atrophic. The epididymis had not yet returned to normal.

Patient 2. This 16-year-old male was awakened on the morning of admission to hospital by pain in the left scrotum. He was flushed, with a temperature of 99°F and on examination the epididymis was found to be enlarged, tender, with no involvement of the rest of the scrotal contents. The urine showed no sign of infection. He was treated conservatively with bed rest and penicillin and streptomycin for 3 days, but because of an unsatisfactory response this was changed to gentamicin for 9 days, followed by oral ampicillin. At this stage local examination revealed a slightly tender, conglomerate mass in the scrotum with no anatomical definition. Because of the suspicion of a testicular tumour, surgical exploration was advised. The spermatic cord appeared relatively normal, with no evidence of torsion; however, the testis and epididymis were black and necrotic and were therefore removed. Histology confirmed the diagnosis of infarction.

Patient 3. The patient, aged 20 years, sustained a gun-shot wound of the bladder and rectum, resulting in a rectovesical fistula. This was treated by sigmoid colostomy and prolonged catheter drainage. The fistula healed spontaneously and the catheter was removed. He was discharged but returned with acute epididymitis which did not settle on conservative therapy. There was marked pyuria, urine culture giving a significant growth of pseudomonas organism. At exploration the spermatic cord was found to be oedematous with constriction at the external inguinal ring. The latter was incised. An epididymotomy was also performed. Postoperatively there was immediate relief of symptoms with improvement of the local signs. When admitted 4 months later for closure of the colostomy, the testis was noted to be markedly atrophied.

Patient 4. This patient, aged 32 years, was admitted with the complaint of a swollen, tender, painful right testis, of 6 days' duration. He had previously sustained a fracture of the pelvis. On examination his temperature was 102°F, the skin of the scrotum was tender and red and the right epididymis enlarged and tender. The urine showed an *E. coli* infection. The spermatic cord was not tender. After 24 hours of conservative therapy there was no improvement and the local signs had deteriorated with tenderness and swelling of the cord up to the external inguinal ring. This was confirmed at surgery and the external ring was incised. An epididymotomy was performed. Postoperatively there was immediate symptomatic relief with marked improvement of the local signs. Cultures taken from the epididymis showed no bacterial growth. A voiding cysto-urethrogram showed a stricture of the membranous urethra. The patient failed to attend for follow-up.

Patient 5. This patient, aged 37 years, was admitted with gradually increasing pain and swelling of the right testis of 5 days' duration, which had not improved on ampicillin. He also had increased frequency of micturition. On examination the scrotal skin was red, the cord thickened and the epididymis enlarged and tender with no involvement of the testis. There was no pyuria and urine culture was sterile. He was treated with bed rest, scrotal elevation and gentamicin 80 mg 8-hourly. He improved during the next 24 hours but on the second day developed marked pain, associated with deterioration of the local signs. At exploration the cord was found to be constricted at the external inguinal ring and the ring was incised. An epididymotomy was not performed. Postoperatively the patient noted immediate improvement. This was accompanied by a fall in temperature from 39.2° to 37.4°C. 5 weeks later there was some epididymal thickening but the testis felt normal.

Patient 6. This 36-year-old patient was admitted complaining of pain in the right testis and a urethral discharge of 7 days duration. On examination the spermatic cord was found to be oedematous and tender, as was the epididymis. He was treated with bed rest and ampicillin but by the following day had more pain, associated with increased tenderness and swelling of the cord. At exploration marked oedema was found to be present in the cord, extending up to the external inguinal ring, which was incised. An epididymotomy was not performed. On the first postoperative day the patient was afebrile and relatively pain-free. He was discharged from hospital 5 days later. He failed to attend for follow-up.

Patient 7. This 23-year-old patient was admitted with a 4-day history of a painful right testis and urethral discharge, for which he had been treated with ampicillin for 3 days prior to admission, without improvement. On examination a swollen, tender right epididymis and spermatic cord were noted. He was treated conservatively for 2 days, during which time there was deterioration of the local signs and symptoms. Exploration revealed marked oedema of the cord extending up to the external inguinal ring, which was incised. An epididymotomy was not performed. The following day he was pain-free and afebrile and was discharged from hospital on his 5th postoperative day. 2 weeks later there was some residual thickening of the epididymis but the testis felt normal.

Comment

The clinical experiences reported here and the evidence in the literature suggests that in acute epididymitis, oedema of the spermatic cord occurs. This inflammatory oedema within the rigid

external ring may cause venous obstruction, culminating in infarction of the testis and epididymis as was demonstrated in Patient 2. A similar pathological sequence of events is well known, for example, in strangulated inguinal hernia. The clinical course in patients 1 and 3 suggests the possibility that lesser degrees of this obstruction, not necessarily leading to infarction, may be the cause of some degree of testicular atrophy. Prompt surgical treatment may prevent both these complications.

Experience gained from this small series has focused attention on certain symptoms and signs which indicate that surgical exploration, with a view to enlarging the external inguinal ring, is necessary. These include particularly

- (1) Testicular pain of sudden onset, often associated with vomiting, which, in character, mimics that of torsion of the testis. The development of this in a patient with acute epididymitis, after an initial period of improvement on adequate conservative therapy, is especially significant.
- (2) Tenderness and palpable thickening of the spermatic cord which persists, or appears during treatment. Whether surgery should be delayed at all when a patient presents initially with this physical sign, is not as yet clearly established. In view of the fact that it probably indicates oedema of the cord, the period of conservative treatment and observation should be limited; if this sign persists or progresses, exploration is indicated. If the sign develops in a patient during conservative treatment and especially if it is associated with increasing pain, surgical exploration should be undertaken with the minimum of delay.
- (3) Deterioration of the local signs represented by increased swelling and tenderness and loss of the ability to distinguish testis from epididymis, especially if this was previously possible. This is a relative indication when encountered on its own but is particularly significant when associated with increasing pain or the development of tenderness and swelling of the spermatic cord. This sign probably explains the misnomer of the term epididymo-orchitis for this condition as the participation of the testis does not necessarily reflect spread of the infection, but is probably secondary to the vascular obstruction at the external inguinal ring.
- (4) Persistent pyrexia during conservative treatment which may be an added indication for surgical intervention.

The validity of this concept of inflammatory oedema of the cord resulting in vascular obstruction at the external inguinal ring, with its consequences to the testis and epididymis, is supported by the sudden improvement in Patients 5, 6 and 7. The response observed also suggests that epididymotomy may not be an essential part of the surgical treatment as in these cases only the external inguinal ring was incised. The scrotal contents were examined to confirm the diagnosis but an epididymotomy was not performed.

This series suggests that surgical exploration of acute epididymitis, with enlargement of the external injured ring, is probably frequently indicated. Whether this more aggressive surgical approach will reduce the incidence of infertility in those patients who have bilateral epididymitis or retain the fertility of the affected organ in unilateral cases will require further investigation.

SUMMARY

7 patients with acute epididymitis, in whom it was found that the rigid external inguinal ring obstructed the blood supply to the testis and epididymis, are described. This resulted in infarction in 1 case and varying degrees of testicular atrophy in the others.

This complication is suggested clinically by an exacerbation of pain, by tenderness and swelling of the spermatic cord and by progressive swelling of the epididymis and testis, in spite of adequate conservative treatment.

Surgical exploration, using an inguino-scrotal incision, is advised to relieve the obstruction by enlarging the external inguinal ring and to explore the testis and epididymis.

This more aggressive surgical approach was of undoubted value in relieving the patient's symptoms and reducing the period of morbidity. Whether it will decrease the incidence of atrophy and sub-fertility in the affected testis, requires further experience.

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Autoantibodies to Spermatozoa in Relation to Male Infertility and Vasectomy

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Cytotoxic antibodies and antibodies which can cause agglutination of spermatozoa may be found in blood or seminal plasma. Both have been intensively studied, and the literature has been reviewed by Hamerlynck (1970). As far as is known, neither type of antibody has any effect upon spermatogenesis; one causes the heads of the sperm to swell up and burst, the other causes the sperms to stick together—so producing the spermagglutination which can sometimes be detected even on a slide of semen if the antibodies are present in sufficiently high titre. Hamerlynck (1967) suggested that there was a relationship between the presence of antibodies which caused the tails of the spermatozoa to stick together and the presence of spermatotoxic antibodies, but that each type of antibody could occur on its own. In our preliminary studies we found that every patient who showed a positive cytotoxic reaction (as defined by Hamerlynck, 1970) also had agglutination of sperm heads in a high titre, but never any tail agglutination.

The prevalence of spermatotoxic antibodies has hitherto not been investigated in large numbers but spermagglutinating antibodies have been exhaustively studied. Rümke (1959) examined the sera from 2,015 men attending an infertility clinic in Amsterdam and found that 3% showed agglutinins in a titre greater than 1 : 32 whereas none of the fertile husbands of 416 pregnant women showed any spermagglutinins in a titre greater than 1 : 16. Sobbe, Haferkamp and Doepfmer (1966) found spermagglutinins in 6% of 150 infertile men, a number closely agreeing with Fjallbrant's findings of 6.7% in 400.

Phadke and Padukone (1964) and Ansbacher, Manarang-Pangan and Srivannaboon (1971) claim that there is an increase in this antibody titre in men who have undergone vasectomy, and suggest that this may cause infertility in men even where successful reconstruction of the vasa has been accomplished by surgical reanastomosis.

We set out to study 3 aspects of this problem, using a combination of techniques which would avoid some of the criticisms which have been levelled against previous work (Hamerlynck, 1970). The first task was the study of spermagglutinating and spermatotoxic antibodies in men known to be fertile, and who had been referred to the vasectomy clinic wishing to be sterilised. The second study concerned the spermagglutinating antibodies in a group of men known to be infertile, who had been referred to an infertility clinic. The third study was on the known fertile men 6 weeks after vasectomy.

Methods and Materials

The techniques used to detect serum spermagglutinating antibodies were those described by Kibrick, Belding and Merrill (1952) but refined and modified in this department (Halim *et al.*, 1973). Cytotoxic antibodies were detected by the method of Hamerlynck (1970) and expressed by his spermatotoxic index (S.T.I.) where a value of 0 to 16 is regarded as negative, of 16 to 25 as doubtful, and more than 25 units as positive. Testicular biopsies and vasography were performed by the methods previously described (Halim *et al.*, 1973). All vasectomies were performed by the same uniform method: 1 to 2 cm of vas was resected within its connective tissue sheath, and each end ligated with 3/0 silk without turning the ends back and without diathermy.

Results

(a) *The Incidence of Spermagglutinating Antibodies and Spermatotoxic Antibodies in Fertile Men referred for Vasectomy*

100 men were examined who had been referred for vasectomy on medical grounds. All were known to be fertile. Five of these men showed some spermagglutinating activity, but only 2 in a titre greater than 1 : 32. Similarly 3 of these also showed some spermatotoxic activity, but only 1 had an STI greater than 25 (Table I). All 3 were known to be fertile—having 2, 2 and 3 children respectively. These findings suggest that even among fertile males there may be a low level of background activity, and that the presence of these antibodies does not necessarily

Table I

Sperm Antibodies in 100 Fertile Males

Titre	Spermagglutinating				S.T. Index	Spermatotoxic		
	Neg.		Pos.			Neg.		Pos.
	0	1 : 4	1 : 20	1 : 32		0	< 25	> 25
No.	95	2	1	2		97	2	1

signify sterility. Rümke and Hellenga (1959) reported finding 4 weak spermagglutinin titres among the husbands of their series of 416 pregnant women, from which they suggested that only a titre greater than 1 : 32 should be regarded as positive.

(b) *The Incidence of Spermagglutinating Antibodies in Infertile Males*

We investigated 144 men referred to the infertility clinic because of childlessness. 21 of them (14.6%) showed sperm agglutination in a titre greater than 1 : 20, and 19 of these (13.4%) in a titre greater than 1 : 32 (Table II). The findings on semen analysis in these 19 patients are set out in Table III. It will be noted that sperm densities ranging from 0 to 250 million per ml were to be found in patients showing positive spermagglutinins.

Testicular biopsies were performed in 5 of these men: 1 showed normal testicular tubules and spermatogenesis; he was azoospermic, and a vasogram was not performed to rule out a mechanical blockage. Two showed aplasia of the tubules: 1 was azoospermic, and 1 had 4 million sperms per ml. Two patients showed sloughing in the tubules—1 was azoospermic and found to have a block by vasography, and 1 had a low sperm count of 5×10^6 /ml.

(c) *The Effect of Vasectomy on the Antibody Titre of 100 Men known to be Previously Fertile*

Spermagglutinins and spermatotoxic antibodies were measured in the same 100 men referred to above (a) 6 weeks after vasectomy. The results (Table IV) show an increase in the numbers showing spermagglutination in a significant 1 : 32 titre from 2% to 6%, while the proportion showing a significant spermatotoxic index increased from 1% to 2%, both in men who also showed spermagglutination greater than 1 : 32. Thus 4 of these men appeared to show sperm-agglutination 6 weeks after the vasectomy when it was not present before.

Discussion

These 3 studies show that there may be a low background level of antibody activity against sperm which is not incompatible with fertility, and that such autoantibodies may be detected in about

Table II

Sperm Agglutinating Antibodies in 144 Infertile Males

Titre	Negative		Positive	
	0	1 : 4	1 : 20	1 : 32
No.	120	3	2	19
%	83.3	2.0	1.3	13.4

Table III

Findings in Infertile Men showing Spermagglutination

Series No.	Spermagglutination Titre	Sperm Density $\times 10^6/\text{ml}$	Motility %
011	1 : 32	0	0
010	1 : 32	0	0
033	1 : 32	0	0
057	1 : 32	0	0

Oligozoospermia

 Oligo. $1 < 20 \times 10^6$

63	1 : 32	5.5	20
47	1 : 32	5	50
84	1 : 32	1	5
5	1 : 32	13	50
9	1 : 32	4	10
73	1 : 32	1	10
70	1 : 32	1	20
85	1 : 20	3	0
41	1 : 20	5	10

Normal sperm density
 $> 20 \times 10^6$

65	1 : 32	90	70
74	1 : 32	50	60
34	1 : 32	100	90
3	1 : 32	59	50
70	1 : 32	70	50
54	1 : 32	250	90

Table IV

Sperm Antibodies in 100 Fertile Males 6 Weeks after Vasectomy

Titre	Spermagglutinating				S.T.I.	Spermatotoxic		
	Neg.		Pos.			Neg.		Pos.
	0	1 : 4	1 : 20	1 : 32		0	< 25	> 25
	No.	90	2	2		6	94	4

2% using the methods described here. This level is increased 6 weeks after vasectomy, but not greatly: *i.e.* from 2% to 6% for spermagglutinins, and 1% to 2% for spermatotoxic antibodies.

Whether these antibodies are of any consequence or not depends upon the association with other antibodies capable of causing systemic disease, or their capacity to make the patient infertile should he at some later date wish to have his vasa joined together again.

In our studies the infertile men did not show a clear pattern by which we could recognise the influence of autoimmunity either in the semen analysis or the histology of the testicle—at least in the small numbers we examined. More of them showed autoantibodies than did the fertile group, and this alone suggests that whatever caused their infertility may have sensitised them to their own spermatozoa. But we do not have sufficient evidence to draw the conclusion that it was the presence of the antibodies which made them sterile. Nor does it follow from the evidence in the literature, or that presented here, that the slight increase in sperm autoantibodies which is seen to follow 6 weeks after vasectomy, implies that the men undergoing vasectomy are also made infertile by reason of these antibodies. This remains a possibility, and one which can only be decided after much more prolonged studies in much larger numbers. Until then, the issue remains unproven.

Summary

In 100 fertile men 2% were found to have sperm-agglutinating antibodies and 1% had spermatotoxic antibodies.

In 144 infertile men 14.6% had spermagglutinating antibodies but these were not clearly related to any particular cause of their infertility.

Six weeks after vasectomy 6% of the 100 fertile men had spermagglutinating antibodies.

The significance and importance of these findings are unknown.

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Treatment of *Pseudomonas* Urinary Infections with Oral Carbenicillin

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Carbenicillin is accepted as an effective non-toxic agent for use in urinary infections with *Pseudomonas* spp. (Turck *et al.*, 1970). Until recently it was available only for parenteral administration, but it has now been shown that the indanyl sodium ester of carbenicillin is absorbed when given orally and rapidly hydrolysed to carbenicillin (Therapeutics Research Division, Pfizer Limited, personal communication).

Infection with low-grade pathogens such as *Pseudomonas* occurs characteristically in patients with an underlying predisposition to urinary infection, such as a structural or neurological abnormality of the bladder. It is favoured by a hospital environment and by previous treatment with antibiotics, and it may occur after instrumentation or catheterisation. Associated renal failure may often be present, making treatment with toxic agents such as gentamicin and the polymyxins hazardous.

We report a therapeutic trial of oral carbenicillin (CP. 15,464) in patients with *Pseudomonas* urinary infection. Because of the common association of renal failure with *Pseudomonas* infection we also report pharmacokinetic data on the drug in patients with impaired renal function, on which published data are scarce (Bailey, Eastwood and Vaughan, 1972).

Therapeutic Trial

Patients and Methods

The Table summarises the clinical, pharmacological and bacteriological data on 8 patients treated with oral carbenicillin.

Infection was diagnosed by finding *Pseudomonas* in a count of at least 100,000 (10^5)/ml in 2 specimens of urine. Carbenicillin sensitivity was ascertained by the blotting-paper disc method (150 µg carbenicillin) and the minimum inhibitory concentration (M.I.C.) of the organism was subsequently determined by tube dilution.

The patients, with one exception, received 4 g. per day of oral carbenicillin in 6-hourly doses. G. S. had slightly impaired renal function, and the dose was reduced to 3 g/day. Treatment had to be stopped in 2 patients (G. S. and C. F.) who developed rashes after 3 and 2 days respectively. Urine specimens were cultured during treatment and at 7 and 21 days after completion of the course. Urine carbenicillin levels were estimated by a large plate assay method, using *Pseudomonas aeruginosa* NCTC 10701 as the standard organism, on several occasions during treatment.

Patients were directly questioned concerning the presence of side effects.

Results

Pseudomonas was eradicated from the urine of the 6 patients who completed the course of treatment. However, in 2 patients (H. K. and J. L.) *Pseudomonas* infection recurred 1 week later; the organisms were still sensitive to carbenicillin *in vitro* and a second course of treatment was given. In 1 patient (H. K.) this was successful and the urine was sterile 1 month later. In the other (J. L.) *Pseudomonas* was again eradicated, but recurred 1 week after stopping treatment.

The first 2 patients treated (S. K. and T. T.) became superinfected with *Klebsiella* while on

carbenicillin, and this organism was subsequently eradicated with co-trimoxazole. In an attempt to avoid superinfection the length of the carbenicillin course given to H. K. was reduced to 7 days, but *Pseudomonas* infection recurred and a second course was required. Of the 6 patients who received a complete course of treatment, 1 (W. G.) died a few days later from bronchopneumonia; 1 (J. L.) had a recurrence of *Pseudomonas* infection; 3 (S. K., H. K. and E. L.) had a sterile M.S.U. 6 to 8 weeks after stopping treatment, and 1 (T. T.) had a low count (10^4) of mixed organisms, not including *Pseudomonas*, 3 months after stopping treatment.

Table

Clinical, Pharmacological and Bacteriological Data on 8 Patients treated with Indanyl Carbenicillin for *Pseudomonas* Urinary Infections

Name	Age	Sex	Clinical Diagnosis	Serum Creatinine mg/100 ml	M.I.C. of <i>Pseudomonas</i> µg/ml	Duration of Treatment (days)	Range of Urine Carbenicillin Levels µg/ml	Side Effects	Outcome
S. K.	75	M	Post-prostatectomy retention of urine	1.2	64	14	317-1975	None	<i>Pseudomonas</i> eradicated. Re-infection with <i>Klebsiella</i>
T. T.	72	M	Urethroplasty for post-prostatectomy incontinence	1.4	128	14	157-1207	None	<i>Pseudomonas</i> eradicated. Re-infection with <i>Klebsiella</i>
H. K.	59	M	Urethroplasty for urethral stricture	1.0	32	7	192-940	Slight diarrhoea	<i>Pseudomonas</i> eradicated but recurred 2 weeks later
					128	14	—	None	<i>Pseudomonas</i> eradicated
W. G.	66	M	Carcinoma of bladder	1.8	128	14	193-1329	None	<i>Pseudomonas</i> eradicated. Re-infection with <i>E.coli</i>
G. S.	66	M	Prostatic hypertrophy Catheter infection	2.9	64	3	97-189	Rash	Treatment stopped (rash). <i>Pseudomonas</i> persisted
C. F.	54	F	Hydronephrotic pelvic kidney	0.8	128	2	—	Rash	Treatment stopped (rash). <i>Pseudomonas</i> persisted
E. L.	66	F	Recurrent urinary infection. Residual urine	0.9	256	14	201-367	Slight diarrhoea	<i>Pseudomonas</i> eradicated
J. L.	62	M	Urethral stricture. Suprapubic catheter	1.5	256	14	487-543	None	<i>Pseudomonas</i> eradicated but recurred 1 week later
					256	14	—	None	<i>Pseudomonas</i> eradicated but recurred 1 week later

Side Effects

Four patients had no side effects; 2 complained of slight looseness of the stools which was transitory and did not necessitate stopping treatment; the remaining 2 developed rashes after 2 to 3 days and treatment had to be stopped.

Pharmacokinetic Study in Patients with Renal Failure

Patients and Methods

10 patients, aged 32 to 73 years, with varying degrees of renal insufficiency were given a single weight-related dose (14 mg/kg body weight) of indanyl carbenicillin orally. No patient with impaired liver function, a positive hepatitis associated antigen reaction or a history of penicillin allergy was included. No patient was receiving any other antibacterial agent at the time of administration or in the immediately preceding seven days.

Samples of venous blood were collected before administration of the compound and at intervals of 1, 3, 5 and 24 hours afterwards. Urine collections were made before the dose, and between 0 and 1, 1 and 3, 3 and 5, and 5 and 24 hours afterwards. In 2 patients with severe renal failure (creatinine clearance 1.8 and 2.1 ml/min respectively) a further urine collection from 24 to 48 hours was made.

Carbenicillin levels were estimated by large plate microbiological assay.

Patients were directly questioned concerning the presence of side effects.

Results

Urine Carbenicillin Levels

Figure 1 shows the urine carbenicillin levels. Six patients with creatinine clearances ranging from 6.6 to 30.6 ml/min achieved levels of over 100 µg/ml whereas the 4 patients with creatinine clearances below 6 ml/min did not.

The average percentage of the administered dose which was recovered in 24 hours from the urine of the 6 patients with creatinine clearances of over 6 ml/min was 12.8 (range 7.6 to 19). This compares with 31.9% (range 10.6 to 49.6) recovered in 24 hours from 13 normal volunteers (Therapeutics Research Division, Pfizer Limited, personal communication). In the 4 patients with creatinine clearances below 6 ml/min, the average percentage recovered in 24 hours was 2.7 (range 0.7 to 6.3). In the 2 with creatinine clearances of 1.8 and 2.1 ml/min from whom urine was collected for 48 hours, the percentage recovered in that time was 1.3 in both cases.

Serum Carbenicillin Levels

The mean peak serum level was higher in patients with impaired renal function than in normal volunteers (Therapeutics Research Division, Pfizer Limited, personal communication), but the peak level attained was never greater than 37.5 µg/ml. However, in the 2 patients with creatinine clearances of less than 4 ml/min, the peak serum levels were only 16 µg/ml and 6.1 µg/ml. These figures, together with the very low percentage of the dose recovered in 48 hours from the urine, suggest that at this level of renal function absorption of the compound is impaired.

Side Effects

No patient in this study complained of any side effects.

Discussion

Indanyl carbenicillin has been shown to be effective in the treatment of *Pseudomonas* infections of the urinary tract in patients with normal renal function. With a dose of 4 g/day, urine levels well above the M.I.C. of the infecting organisms were achieved. Whilst this trial was in progress, all *Pseudomonas* spp. isolated from specimens of urine in this laboratory were tested for sensitivity to carbenicillin. Of the 51 strains isolated, 44 were sensitive using the blotting-paper disc (150 µg carbenicillin) method. The M.I.C. of these strains, and of 2 strains isolated from other specimens, was determined by tube dilution. 13 strains had an M.I.C. of 256 µg/ml and the remaining 33 strains had an M.I.C. of 128 µg/ml or less. It seems likely, therefore, that urine levels of carbeni-

cillin after oral administration of the indanyl ester are adequate for treatment of the majority of *Pseudomonas* infections in the urinary tract. Even in patients with considerable impairment of renal function (creatinine clearance down to 6 ml/min) a single oral dose of 14 mg/kg produced a concentration in the urine sufficient to inhibit the growth of at least two-thirds of the *Pseudomonas* strains isolated in this laboratory, and did so within 6 hours when the urine level was probably still rising. It is likely, therefore, that in this range of renal function a dose schedule could be designed to maintain bactericidal levels for nearly all strains of *Pseudomonas* in urine. However, with creatinine clearances below 6 ml/min it is evident that absorption cannot be relied upon.

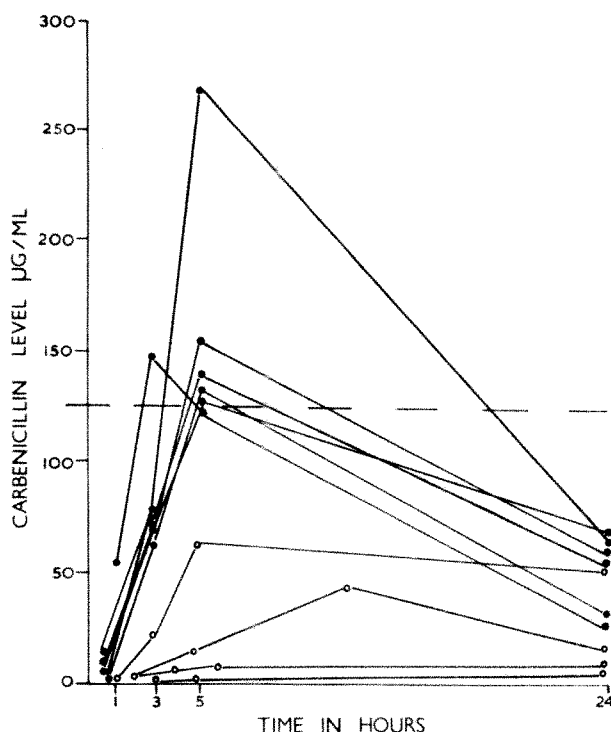


Fig. 1. Urine carbenicillin levels in 10 patients with renal insufficiency after a single weight-related dose of indanyl carbenicillin.
 ●—● Patients with creatinine clearances of over 6 ml/min.
 ○—○ Patients with creatinine clearances of less than 6 ml/min.
 — 128 µg/ml. The M.I.C. for two thirds of *Pseudomonas* spp. falls at or below this level.

Studies on normal volunteers (Therapeutics Research Division, Pfizer Limited, personal communication) have shown that the serum levels attained in the presence of normal renal function are inadequate for the treatment of systemic *Pseudomonas* infections. In patients with renal failure the peak serum levels after a single dose are higher than those in normal volunteers, but are still well below those required to inhibit *Pseudomonas*. As high serum levels of carbenicillin are known to be tolerated well (Garrod and O'Grady, 1972) it is possible that therapeutic serum levels might be attained by administration of a suitable dose schedule to patients with impaired renal function; the present study, however, does not provide any evidence about this.

Pseudomonas was eradicated from 5 of the 8 patients, though 1 required a second course. Two more might have been successfully treated had not rashes curtailed their treatment. Superinfection with *Klebsiella*, a recognised complication of the use of penicillins in vulnerable patients such as these, need not prevent the use of indanyl carbenicillin, since *Klebsiella* can be eradicated

satisfactorily with nitrofurantoin or co-trimoxazole. This complication might be less likely to occur if carbenicillin were given for 7 days only; however, the 1 patient in this trial who had a 7 day course had a recurrence of *Pseudomonas* infection. Alternatively, a small prophylactic dose of co-trimoxazole, say one tablet at night, might be given concurrently.

The dangers of using toxic agents such as gentamicin and the polymyxins in patients with impaired renal function are well recognised, and *Pseudomonas* infections in such patients can be treated with carbenicillin with much greater safety. This study suggests that, even when renal function is considerably impaired, oral administration of the indanyl ester of carbenicillin is likely to be effective in the treatment of urinary infections.

We agree with Wallace and his co-workers (1970) that the use of the oral form of carbenicillin should be restricted to the treatment of *Pseudomonas* and indole-positive *Proteus* infections confined to the urinary tract. Its widespread use for other urinary infections might well limit the usefulness of parenteral carbenicillin "by causing selection of resistant strains of *Pseudomonas* in hospitalised patients" (Wallace *et al.*, 1970). There is a variety of effective oral agents available for treatment of urinary infections due to the common pathogens.

Summary

A trial of oral carbenicillin for the treatment of *Pseudomonas* urinary infections in 8 patients is reported. *Pseudomonas* was eradicated in 6 patients, but recurred in 1. Treatment had to be curtailed in the remaining 2, who developed rashes.

In a pharmacokinetic study of 10 patients with varying degrees of renal insufficiency it was shown that levels of carbenicillin likely to be adequate for the treatment of *Pseudomonas* urinary infections were attained in patients with creatinine clearances of over 6 ml/min. With clearances below this level there was evidence that absorption was impaired, and adequate urine levels were not achieved.

It is suggested that the use of oral carbenicillin should be restricted to the treatment of *Pseudomonas* and indole-positive *Proteus* infections confined to the urinary tract.

We are grateful to Dr E. H. Minors, Mr J. Vinnicombe and Mr G. F. Abercrombie for permission to treat their patients, and to the Clinical Research Department, Pfizer Limited, for financial support and for providing supplies of CP 15,464. (Requests for reprints should be addressed to R. M.)

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Short Case Reports

Secondary Melanoma of Ureter

A 65-year-old woman presented in April 1964 with malignant melanoma of left leg without evidence of metastasis. The lesion was widely excised. One and a half years later, a local recurrence slightly proximal to the previous site was excised. Blood pressure ranged from 160/90 to 180/110 with no symptoms. At this stage lymphangiography showed subclinical nodal invasion and lymphatico-portal anastomosis. Intra-lymphatic radioactive gold treatment was given. In 1966 further local recurrences developed and were widely excised and a combination of Malphalan and deep X-ray treatment was given.

Satisfactory remission was maintained until August 1969 when she presented with haematuria, hypertension (B.P. 230/130) and headache. An I.V.P. revealed a non-functioning right kidney. At cystoscopy the bladder appearances were normal and a right retrograde urethro-pyelogram revealed obstruction in the upper third of the ureter due to a tumour (Fig. 1). A right nephro-ureterectomy was performed. The naked-eye appearance of the specimen showed a pigmented tumour arising and projecting into the lumen of the upper third of the right ureter causing hydronephrosis. There was a further pigmented deposit in the lower third of the ureter (Fig. 2). At operation no visible or palpable evidence of metastasis was seen elsewhere. The histological examination confirmed the tumour to be secondary melanoma of the ureter. The B.P. noted 2 months after operation was 160/90. The patient died 6 months later following a cardiovascular accident. An autopsy was not performed.

This appears to be the ninth reported case of secondary melanoma of the ureter.

The Author

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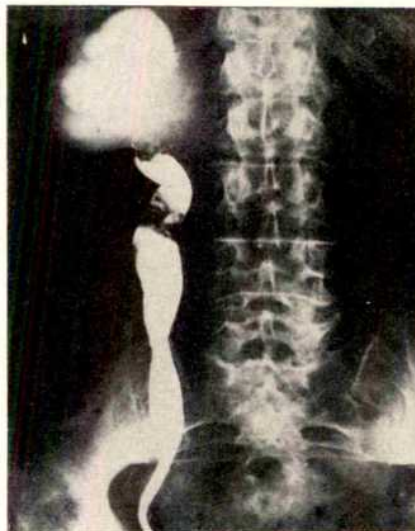


Fig. 1



Fig. 2

Webbed Penis

A boy of 5 presented at hospital for circumcision. His own doctor had refused to do the operation because of a congenital abnormality of the boy's penis. When it was elevated a web of skin was drawn up on its under surface from the scrotum, masking the outline of the penis (see Figure). Circumcision was done together with excision of the web. After excision of the web the penile part of the wound was sutured longitudinally but the scrotal part transversely to avoid a pendulous scrotum.

Mason Brown (1962) described the surgical correction of the abnormality as either the use of a Z-transposition plastic procedure or by the preliminary penile lengthening operation when there is associated hypospadias. The embryological explanation of webbed penis may be that there is a partial failure of the posterior migration of the labio-scrotal folds.

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Reference

MASON BROWN, J. J. (1962). *Surgery of Childhood*, 1st ed. p. 1160. London: Arnold.



Webbed penis.

Book Reviews

Uremia. Edited by R. KLUTHE, G. BERLYNE and B. BURTON. Pp. xiii + 312 with 178 illustrations. London: Churchill Livingstone. 1972. £8.00.

This is the proceedings of an international conference which was largely devoted to the pathogenesis and dietary treatment of uraemia. It contains 44 papers and what would appear to be almost verbatim reports of the discussions which followed each session. Many of the papers are based on laboratory studies involving the use of advanced and highly sophisticated biochemical and physiological techniques, but few are at all conclusive and it is evident, particularly from the opening papers on uraemic toxins, that uraemia is not going to yield tamely to the assault of modern research.

Indeed it would seem permissible to venture the opinion that the application of increasingly advanced techniques of analysis to the study of uraemia might well bring more confusion rather than clarification to a topic which is already confusing enough. Although the later sections on the use of low protein diets contain a number of papers of clinical interest, the book as a whole will be of more value to the research biochemist or physiologist than to the clinician.

It is well produced but, bearing in mind that the proceedings of an international conference are likely to date even more rapidly than other forms of medical literature, rather expensive.

A. R. H

The Kidney. By JAN BROD. Pp. 613 + 127 with illustrations. London: Butterworths. 1973. £28.00.

This outstanding and intensely readable book, representing as it does the distillate of knowledge gained by 35 years of devotion to the study of the kidney by one of the world's foremost authorities, seems destined to become one of the great medical monographs of the 20th century. The book's appearance is an especially happy event for those who have enjoyed and benefited from Professor Brod's writings in the past. Unassisted by the contributions of several different experts the author has been able to preserve a coherence and uniformity almost impossible to achieve with a multi-author textbook.

Part I, approximately one third of the book, is devoted to renal physiology in all its aspects starting with the evolution of the human nephron from primitive forms of life. In a masterly exposition of renal micro-anatomy and physiology, assisted by numerous beautiful illustrations the author demonstrates his supreme ability to explain difficult concepts clearly. Well chosen subtitles and summaries at the end of each section make it easy to use the book as a work of reference.

The natural history of the main renal diseases occupies the second part of the book. Vivid and accurate descriptions give the impression of a highly sensitive clinician with a vast personal experience not only of nephrology but of all aspects of general medicine. There are splendidly lucid reviews on hypertension including renal and renovascular hypertension, nephrotic syndrome, glomerulonephritis and pyelonephritis. The third part goes on to discuss the author's clinical approach to disease states. The use of simple renal function tests to distinguish predominantly glomerular and tubular lesions is fully exploited, and the common as well as the rare renal lesions are comprehensively covered. Inevitably certain parts show a lack of balance reflecting the personal interest of the author—for example the beautifully detailed description of renal tuberculosis, a comparatively rare condition in advanced societies, dwarfs the somewhat sketchy account of the nephropathy of gout, which must now be seen much more frequently. Such observations in no way detract from the value of this work which, by the author's own admission, was not intended to be a manual of instruction.

The chapter on renal calculi will be of particular interest to urologists, especially the theories on the genesis of calculus formation, but it is surprising that no mention is made of the use of allopurinol in the prevention of urate calculi. In the management of renal failure many will disagree with the author's recommendations to employ regular blood transfusions, routine antibiotic prophylaxis, or tetracycline as a routine additive to peritoneal dialysis solution. These minor criticisms, however, shrink to the status of petty quibbling when seen against the background of unsurpassed clinical wisdom of the book as a whole. Physicians, surgeons, and physiologists whose interest lies in the kidney have been bequeathed a priceless classic whose teachings are likely to endure for a long time.

P. R. U.

Urinary Infection. By T. A. STAMEY. 1st Edition, Pp. xvi + 293. Baltimore: Williams and Wilkins Co. 1972. £9.00.

Following the impetus generated by E. H. Kass in 1956, there has been an enormous amount of research into the aetiology and management of infections of the urinary tract. Up to now there has been no ready access to this wealth

of material. However, Professor Stamey has rectified this serious omission in our medical literature. He has brought together nearly all the relevant literature and has presented it in detail and discussed it thoroughly, critically and objectively so that his recommendations on the diagnosis and management of urinary tract infections are well substantiated. Obviously there is the inevitable personal bias towards those aspects of research to which he has particularly devoted himself such as the pathogenic role of bacterial colonisation of the vaginal introitus, and perhaps he has over emphasised the importance of this stage in the development of urinary tract infection. Similarly, the simple uncomplicated natural history of so many urinary tract infections is under emphasised, in fact doubted, presumably since it is not seen in hospital practice. However this is minor criticism of what is a comprehensive review of a vast field of medical literature carried out with full scientific objectivity and with unusual scholarship.

The particular strength of this book is the synthesis it presents between bacteriology and clinical medicine. For example the chapter on antimicrobial sensitivity testing shows a better understanding of this problem and its clinical limitations than is seen in many a bacteriological textbook. It is therefore a pity with this depth of knowledge of bacteriology, that the first chapter on the diagnosis of bacteriuria should be somewhat dated in recommending now, even for consulting room use, a 0.1 ml dropper technique instead of a disposable loop delivering a hundredth of this amount or the use of dip-slides. The clinical histories presented to emphasise the problems encountered in treating chronic bacterial prostatitis, urinary infection in the presence of stones or in the presence of urological abnormalities are extremely interesting as well as being instructive. This is anecdotal teaching at its very best, especially when linked with so complete an understanding of the laboratory investigations used.

The reviews of asymptomatic as well as symptomatic urinary tract infection in non-pregnant women, in infancy and childhood and in pregnancy are comprehensive and there is a particularly well reasoned argument for a conservative approach in the management of ureteric reflux.

The chapter on therapeutic principles is again well thought out and argued, though the recommendation that benzyl penicillin be regarded as the broad spectrum antibiotic of choice would not be widely accepted. It is surprising that there is no discussion of the simultaneous use of more than one antibacterial agent other than in the use of the combination, cotrimoxazole. The intractable problems Professor Stamey describes in treating infections with *Proteus* organisms would perhaps benefit from the use of combination chemotherapy and this should at least have been discussed. This is the only serious omission in what is otherwise an exceptional monograph which will make interesting and valuable reading for doctors in many different disciplines. It could well become obligatory reading for all nephrologists and urologists as well as those physicians and bacteriologists who are seriously interested in urinary tract infections.

J. B. S.

Books Received

Blutgerinnung und Operation. By E. DEUTSCH. Munich: Urban and Schwartenberg. 1973. DM.42.

Pituitary Tumours. By J. S. JENKINS. Pp. 206 with illustrations. London: Butterworths. 1973. £5.

Preliminary Announcement

X CONGRESS OF THE EUROPEAN SOCIETY FOR EXPERIMENTAL SURGERY

PARIS, 6th to 9th APRIL 1975

The 10th Meeting of the European Society for Experimental Surgery will be held in Paris on 6th to 9th April 1975.

CONFERENCES AND COURSES

Institute of Urology (University of London) in association with St Peter's Hospitals

AUTUMN TERM, 1973

1-day Symposium on **Urothelial Neoplasia**, Saturday, 20th October—Fee £8

4-day combined Course in Nephrology—

Scientific Aspects of Renal Disease (jointly with Institute of Basic Medical Sciences),
Tuesday, 20th November

Membership Course in Nephrology, Wednesday and Thursday, 21st and 22nd November
Hypertension, Friday, 23rd November

2-day course **Uro-Radiology Weekend**, Saturday and Sunday, 15th and 16th December—Fee £12

Further information and detailed programmes may be obtained from The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London, WC2H 8JE.

MISS MURIEL JONES, M.A.

and the

INDEX TO CURRENT UROLOGICAL LITERATURE

This is the last Index to Current Urological Literature to be compiled by Miss Muriel Jones who has provided this service since the British Journal of Urology was founded in 1929.

Miss Jones took an honours degree in modern languages at Girton College, Cambridge, in 1915 and a few years later joined the staff of the Library at the Royal Society of Medicine. Here she has worked for the Journal for the past 44 years without a break, even during the war. The work has been unremitting and exacting, dealing with a continuous inflow of journals which in recent years has amounted to about 50 issues a day. Miss Jones is now 80 and has decided to retire.

On May 21st a small luncheon party was held at the Royal Society of Medicine to mark her retirement and to express the gratitude of all those concerned with the Journal for this long service of such consistently high quality. The Editorial Committee was represented by the Chairman, the Editor and the London members of the Executive Committee. Miss Jones was presented with a cheque and a silver medal bearing the crest of the Journal and, on its reverse side, an inscription expressing the appreciation of the Editorial Committee.

B. H. P.

INDEX TO CURRENT UROLOGICAL LITERATURE

BLADDER

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VAS DEFERENS

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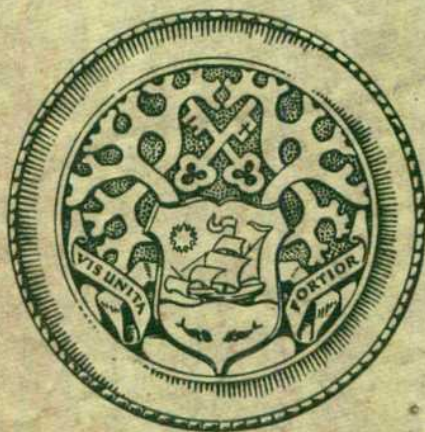
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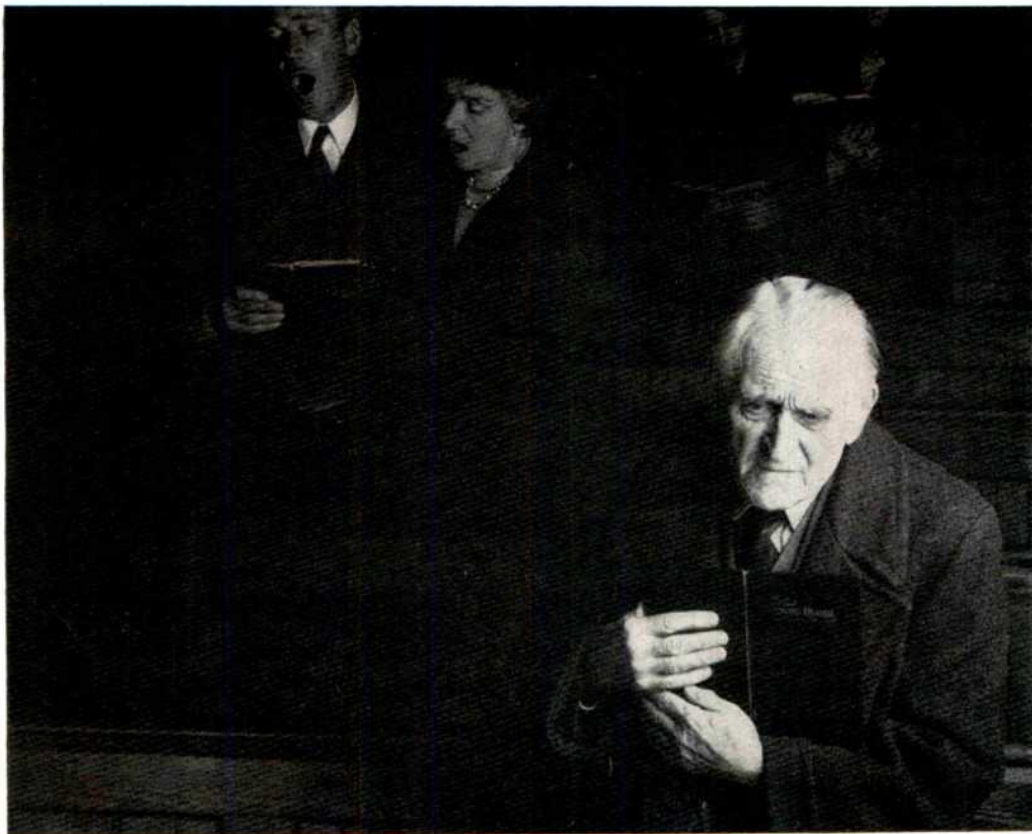


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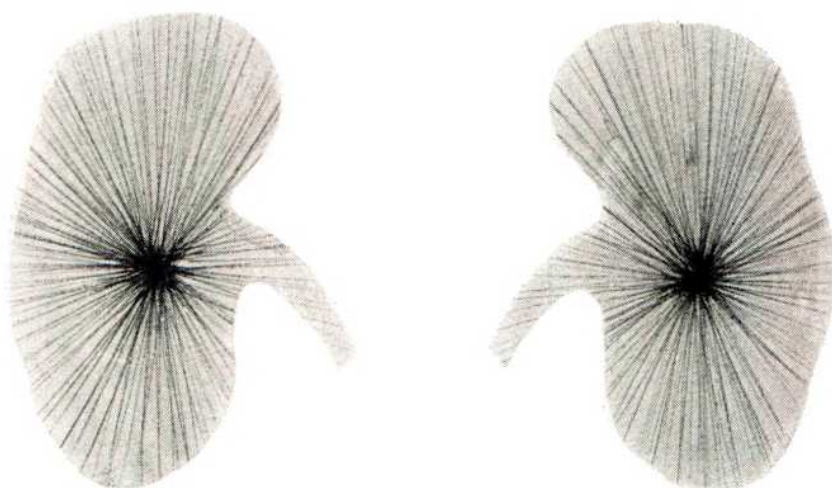
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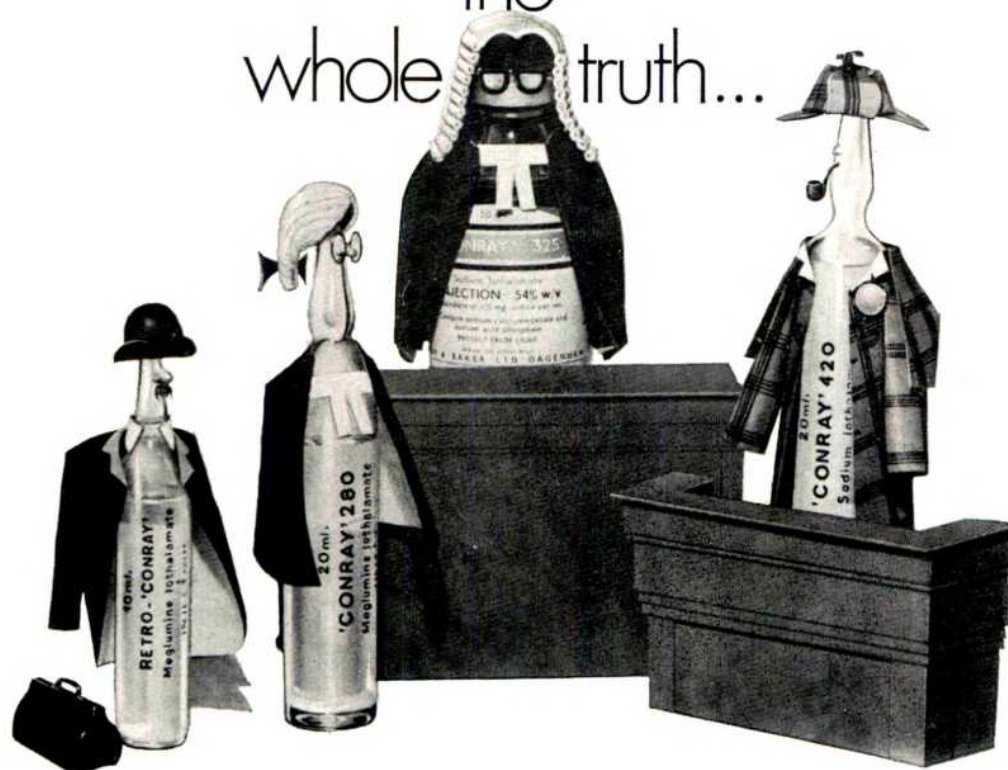
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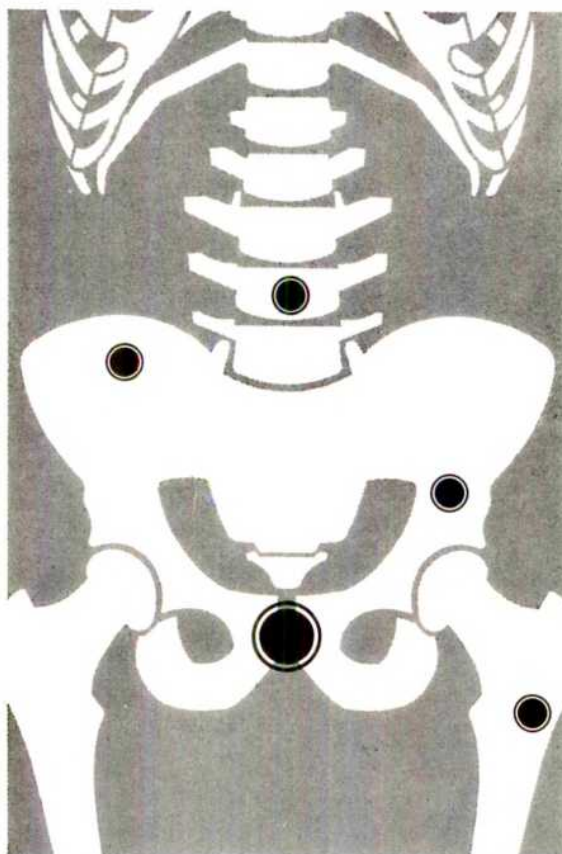
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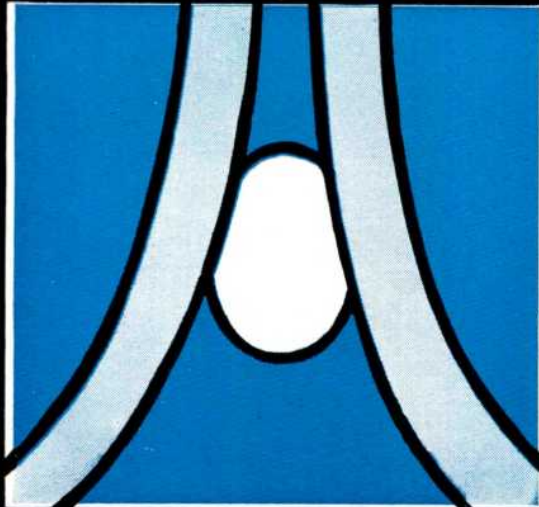
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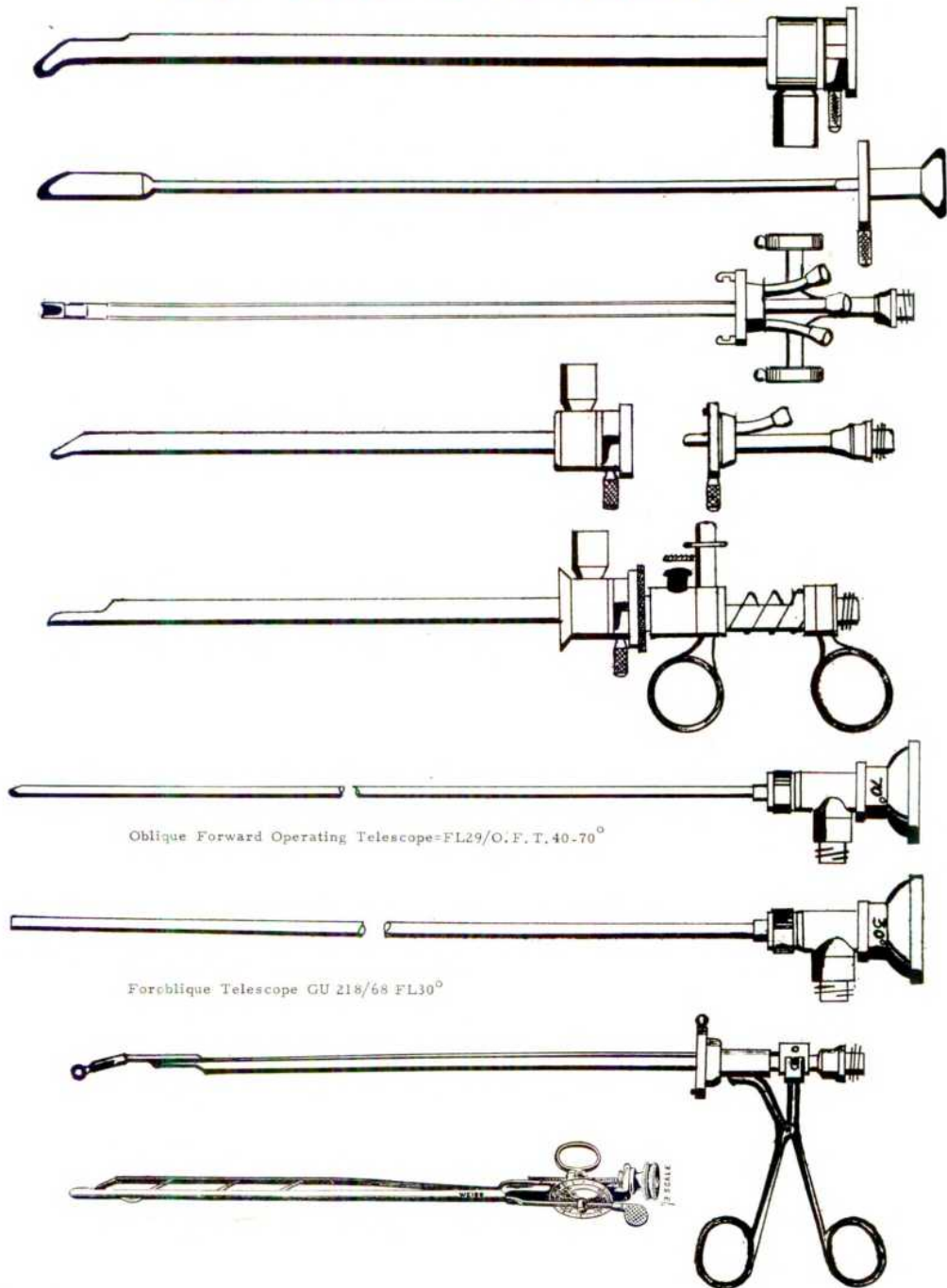


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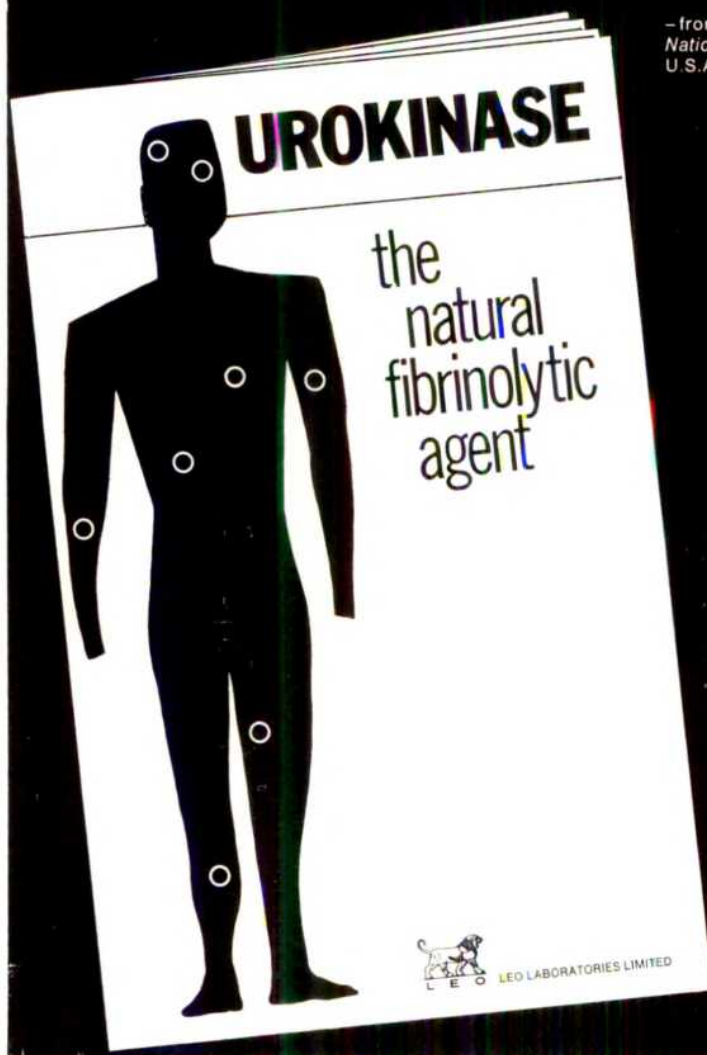


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References: (1) J. Urol. (1969) 102:699 (2) Brit. Med. J. (1970) 2:643 (3) Brit. Med. J. (1972) 1:285 (4) Arch. Derm. (1971) 104:508 (5) Cancer (1971) 28:1142 (6) Ugesk. for Laeg. (1971) 133:335.

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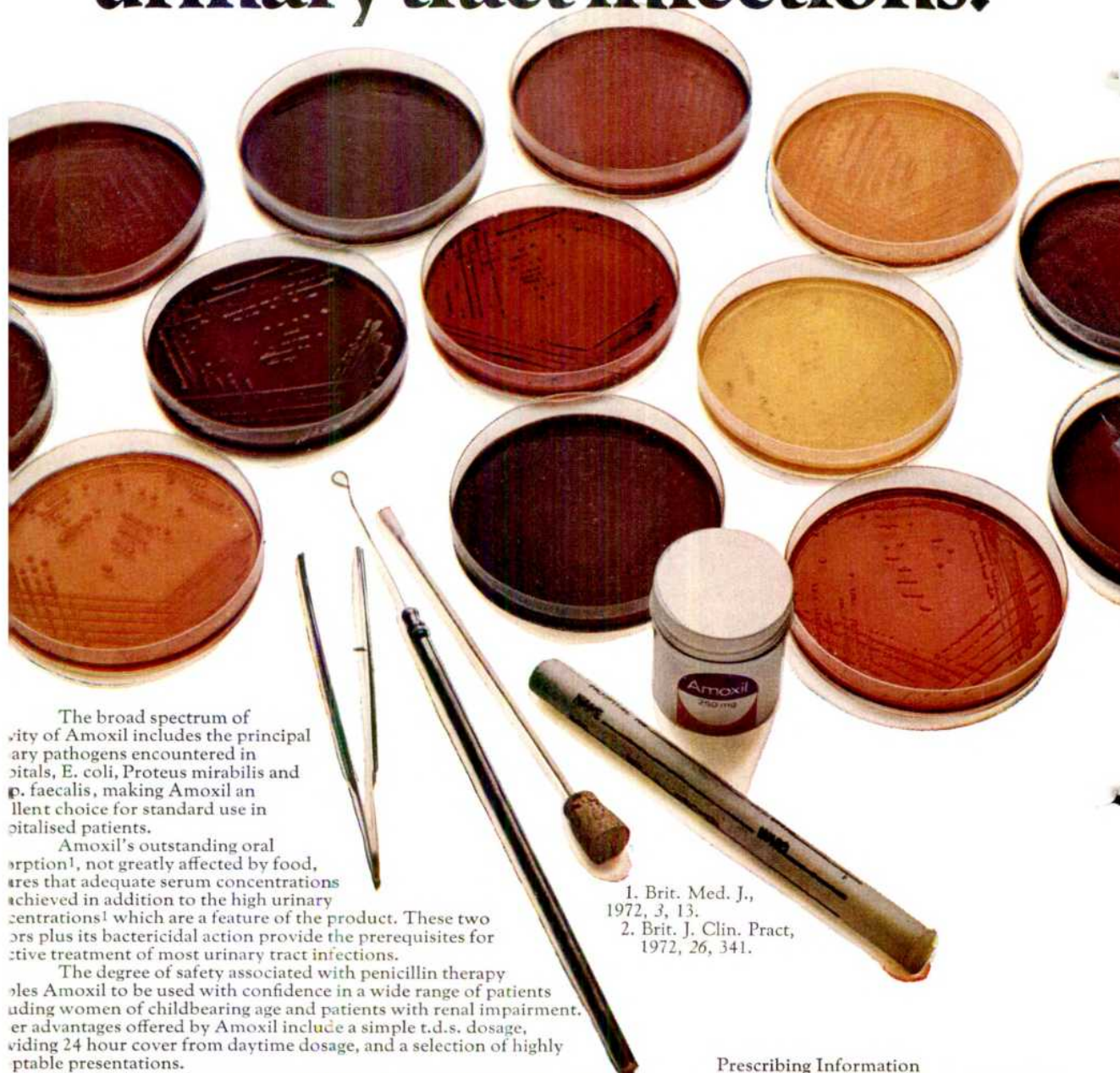


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1. Brit. Med. J., 1972, 3, 13.

2. Brit. J. Clin. Pract., 1972, 26, 341.

Prescribing Information

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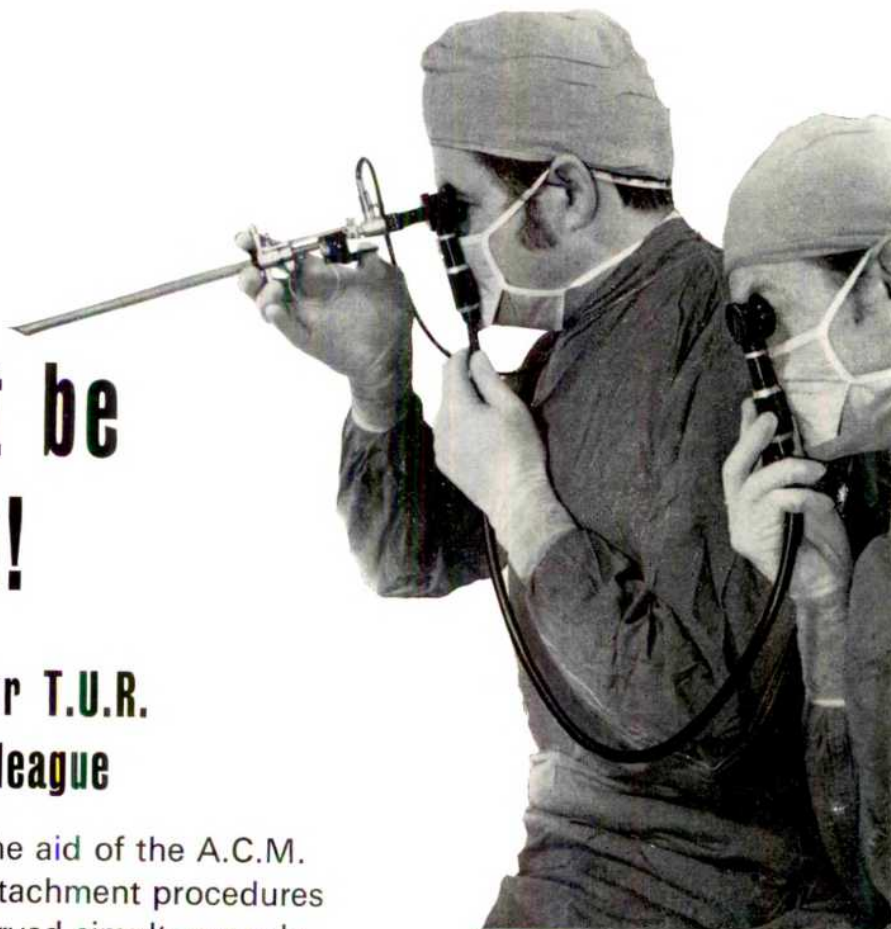
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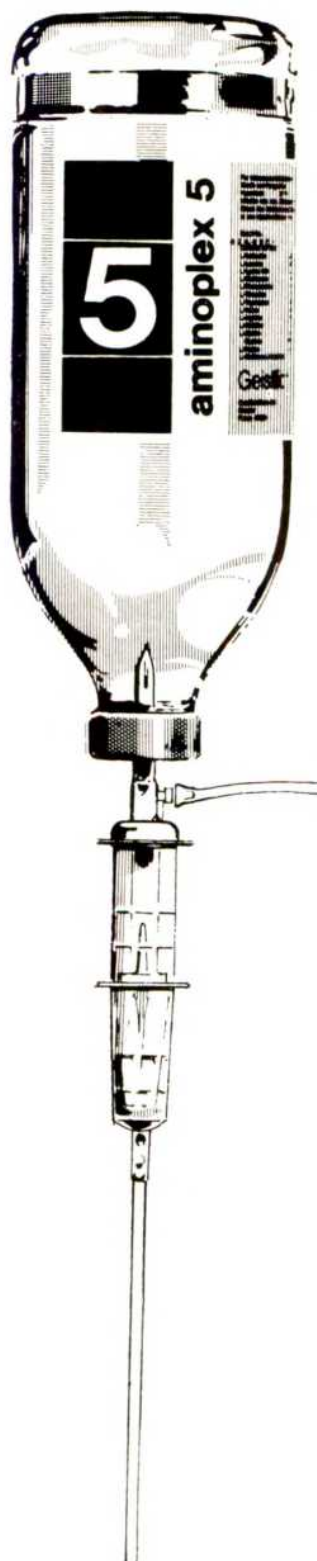
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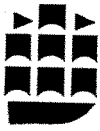
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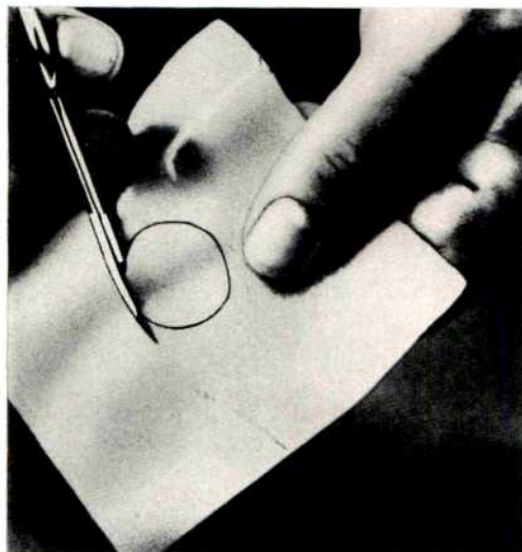
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Preliminary communications of original work may be submitted as short papers. The communication should be divided into 4 sections: (1) Objectives, (2) Materials and Methods, (3) Preliminary results, (4) Interpretation or Significance of Results.

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Questions or criticisms concerning recently published papers may be sent to the Editor, who will refer them to the authors. The readers' comments and authors' replies may subsequently be published together.

There is no other correspondence section in the *Journal*.

Suggested Projects for Urological Research

Clinicians who have ideas for research projects, but have no opportunity for carrying them out, may submit them for publication in the above section. The communication should not be longer than 500 words. References will be limited to 6.

Abstracts from Current Urological Literature

Urologists who are willing to undertake abstracting of urological articles appearing in other journals should communicate with the Assistant Editor, Mr W. Selby Tulloch, indicating in which language(s) they are proficient.

Addresses

With the exceptions noted below, all editorial communications, including books for review, should be addressed to the Editor, Mr W. Keith Yeates, at the Department of Urology, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE.

Preliminary Communications on Research Projects and Suggested Projects for Urological Research should be submitted to the Assistant Editor, Mr G. D. Chisholm, at The Urology Unit, Hammersmith Hospital, Royal Postgraduate Medical School, London, W12 0HS.

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BRITISH ASSOCIATION OF UROLOGICAL SURGEONS

(Home and Overseas)

SIMPLA UROLOGICAL PRIZE

A prize of £200 is offered by Simpla Plastics Limited for an essay on "Disposable Equipment in the Urological Field—Desirable Standards and Thoughts on Future Development".

The essays will be judged by the President of the Association for 1973-74, a Urologist named by the Association and a Urologist selected by Simpla Plastics Limited.

Ten copies of the essay marked with a suitable pseudonym, together with the name and address of the entrant and his pseudonym on a separate sheet, should be submitted to the Honorary Secretary, the British Association of Urological Surgeons, at the Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London, WC2A 3PN by 31st March 1974. The essay may be published at the discretion of the Editor of the *British Journal of Urology*.

The award, which may be taken either as a cash payment or as a Travelling Fellowship, will be announced at the Annual Meeting of the Association in June 1974.

THE BRITISH ASSOCIATION OF UROLOGICAL SURGEONS

THE TWENTY-NINTH ANNUAL GENERAL MEETING was held in the Edward Lumley Hall, The Royal College of Surgeons of England, Lincoln's Inn Fields, London, WC2A 3PN on WEDNESDAY, 27th JUNE, 1973 at 2 p.m.

The President, Mr Howard G. Hanley, was in the Chair.

1. Minutes of the Annual General Meeting held on 5th July 1972 in Newcastle upon Tyne, which had been circulated, were taken as read and signed as correct.

2. Election of New Members. The following were elected Full Members on the nomination of the Council: Mr C. P. Bates, Nottingham; Mr J. C. Gingell, Bristol; Mr R. W. Glashan, Huddersfield; Mr E. S. Glen, Glasgow; Mr W. F. Hendry, London; Mr W. G. G. Loughridge, Belfast; Mr J. A. MacDougall, Wolverhampton; Mr M. H. E. M. Mostafa, Canada; Mr R. G. Notley, Guildford; Mr R. W. M. Rees, Cardiff; Mr M. J. Rochford, Australia; Mr P. J. B. Smith, Bath; Mr H. F. R. Story, Australia; Mr C. P. Taneja, India; Mr A. P. Tynan, Australia; Mr R. H. Whitaker, Cambridge.

3. Report of Council for 1972/73. The Report of Council for 1972/73 which had been circulated, was received and adopted.

4. Report of the Honorary Treasurer and Balance Sheet to 31st December 1972. The audited accounts for the year 1972 which showed a profit on the year's working of £2,233.79, were presented by the Honorary Treasurer and approved.

5. Amendments to the Rules. On the recommendation of the Council, it was agreed that the following amendments should be made to the Rules:

Rule 3 "Membership": "Pakistan" should be inserted after "South Africa".

Rule 3 (c) Affiliated Members: that the following paragraph be deleted from the Rules: "Candidates for Affiliated Membership, holding a reasonable medical qualification, may hold an honorary appointment at registrar level".

Rule 3(d) Senior Members: A Full Member who has reached the age of 65 shall automatically become a Senior Member. A Full Member, retiring before the age of 65, will be eligible for election to Senior Membership. Council is empowered to elect Associate Members on retirement to Senior Membership on an *ad hoc* basis. Senior Members shall pay no annual subscription and shall not receive the *British Journal of Urology*.

6. Election of Officers. The following were elected Officers for 1973/74:

<i>President:</i>	Mr Howard G. Hanley
<i>Vice-President:</i>	Mr R. A. Mogg
<i>Honorary Treasurer:</i>	Mr Thomas Moore
<i>Honorary Secretary:</i>	Mr J. P. Williams
<i>Honorary Editorial Secretary:</i>	Mr W. Selby Tulloch

7. Election of Members of Council. It was reported that the following had been nominated for election to the Council:

Full Members:

Professor J. P. Blandy
Mr Norman Gibbon
Professor John Swinney } by the Council

Mr J. B. M. Roberts nominated by Mr J. P. Mitchell and Mr Norman Slade

A ballot was held and the following were elected to fill the vacancies: Professor J. P. Blandy, Mr Norman Gibbon, Professor John Swinney.

8. Associate Member Representative on the Council. Mr James H. Levack was elected to fill the vacancy on the Council for an Associate Member Representative.

9. Election of Auditors. Messrs Howard, Tilly and Co. were re-elected auditors for the ensuing year.

10. 1974 Annual Meeting. It was reported that the 1974 Annual Meeting would be held in Torquay from 26th-28th June. The President stressed the importance of Members arranging accommodation at the Imperial Hotel as early as possible.

11. **1975 Annual Meeting.** It was reported that the 1975 Annual Meeting would be held in Cardiff.

12. **1973 Provincial (One-day) Meeting.** It was reported that the 1973 Provincial (One-Day) Meeting would be held in Birmingham on 13th October.

13. **Standing Committee on the Development of the Urological Services.** Mr D. Innes Williams, Chairman of the Standing Committee on the Development of the Urological Services, reported on the efforts of the Standing Committee to obtain more and better urological departments throughout the country. During the past year, the Committee had invited one or two representatives from a region to discuss the urological situation in their respective areas. Due to the re-organisation of the Health Service, many regions had delayed making decisions, but reports from the North-East Metropolitan region were very favourable and Mr Moore of the Manchester region was to be congratulated on the work carried out there.

The Committee had discussed the problem of the "General Surgeon with an interest in Urology", particularly in relation to the South-West Region and the Oxford Region where, with a number of small towns with District General Hospitals, the general surgeon with an interest played an important role. Members of the Standing Committee considered it vitally important that any general surgeon with an interest in urology appointed should receive an adequate training in urology. Mr Innes Williams asked all Members of the Association invited to serve on Appointments Committees to ensure that such a level of training had been attained by the successful candidate because, even in the past year, this had not always been the case. The Committee felt that for the general surgeon with an interest in urology, a minimum of 2 years training in urology was obligatory; it was impossible to obtain adequate endoscopic experience in less than this time.

Following the letter from the Central Manpower Committee, Mr Innes Williams said that the problem of re-distribution of Senior Registrars had to be faced. He felt that such re-distribution would be beneficial and the Association should endeavour to facilitate this move. It was the Association's responsibility primarily to ensure that there were enough trainees to take over all the new appointments they hoped to gain and to maintain the balance between registrars; also to ensure adequate training in good centres, distributed evenly throughout the country.

Mr Roberts of Bristol said he was unhappy about the 3-year training programme for a specialist urologist and asked the Standing Committee if, in an average sized hospital, they wished to replace the general surgeon with an interest in urology by a urologist working on his own; for in his opinion, a minimum of two urological surgeons was essential. He also questioned whether Senior Registrars in general surgery would wish to spend 2 years in a urological department, and suggested that 6 months might be more reasonable.

Mr Innes Williams said that these problems were clear to the Standing Committee and he told Members that they would have an opportunity to voice their opinions on training in general at the One-Day Meeting in the autumn. He agreed that the single specialist urologist was not a satisfactory situation and if this occurred, he should be teamed up with a general surgeon with an interest in urology. Although in many small hospitals this wasn't always possible, he hoped with the anticipated increase in the number of consultants, that this could be achieved.

With regard to the length of training for the general surgeon with an interest, he agreed there were objections on both sides and the Association would have to accept a compromise. The Association could not lay down hard and fast rules as such appointments were in the hands of Regional Authorities, but there were some standards which had to be determined.

14. Any Other Business

(a) **Urological Prize.** It was reported that Simpla Plastics Limited had offered a "Simpla Urological Prize" to the value of £200.

(b) **Department of Venereology.** It was reported that a letter had been received saying that a Department of Venereologists wished to refer to their department as Genito-Urinary Medicine. Members of the Association strongly disapproved of this.

Renal Artery Thrombosis

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When Evans and Mogg in 1961 described a case of renal artery thrombosis due to closed trauma they could find only 13 other cases in the literature. The increasing use of renal angiography has produced a growing awareness that renal artery thrombosis is not in fact rare. Cornell, Reasa and Culp (1972) reported 5 patients with traumatic occlusion of the renal artery seen in Iowa City in a 5 year period and Sullivan, Smalley and Banowsky (1972) reported 6 cases of renal artery occlusion secondary to blunt trauma.

The condition can also occur spontaneously as in 2 of the 4 cases reported here.

Perhaps the most important feature of renal artery thrombosis, whether traumatic or spontaneous, is that it causes hypertension but the relationship of the hypertension to the thrombosis and the mode of onset of the hypertension can vary to an extraordinary degree.

A 24-year-old fireman fell 30 feet and was admitted to hospital with a ruptured spleen. It was known from routine medical examination that he had been normotensive up to 1 week before the accident. His spleen was removed but kidney injury was not at that time diagnosed. However, in the 4 weeks following his injury he developed a fulminant malignant hypertension. Intravenous pyelogram showed a normal right kidney but no excretion on the left side. A left retrograde pyelogram was normal. Renal angiography disclosed complete thrombosis of the left renal artery. His blood pressure returned to normal immediately after removal of the left kidney and has remained normal in the ensuing 10 years. It was interesting that the kidney was completely necrotic except for a very thin rim, no more than 1 mm thick, just under the renal capsule.

Geyskes and his colleagues (1972) have shown that malignant hypertension can equally follow obstruction of a branch of the renal artery but this is not always so.

Figure 1 shows the nephrogram phase of a selective arteriogram in a man aged 35 who suffered traumatic infarction of the upper half of his left kidney in September 1972. The lower half of the kidney functions well and to date (June 1973) his blood pressure remains normal.

Spontaneous renal artery thrombosis can be equally variable in its relation to hypertension and also in its clinical presentation.

A 50-year-old farmer presented in December 1971 with vomiting and headaches for a period of 6 weeks. There was no previous medical history and no other symptoms. He was found to have malignant hypertension with a diastolic blood pressure of 120 mm Hg. An intravenous pyelogram showed no excretion on the right side but a right retrograde pyelogram was normal. Angiography revealed total obstruction in the right renal artery beginning 0.5 cm from the aorta.

The right kidney was removed at the beginning of March 1972. The blood pressure dropped suddenly to 90/60 as soon as the kidney was removed—indeed it took 2 days to return to normal levels and there was a transient renal failure with a rise of creatinine to 3.5 mg %. His blood pressure stabilised at normal levels and the kidney function returned to normal. In the past year he has remained completely well and normotensive.

This complete thrombosis of the renal artery may have been the end result of a renal artery stenosis but serial sections of the artery revealed only organised thrombus and no other vascular disease. In this case there were no symptoms other than the symptoms of the malignant hypertension but the clinical presentation of a spontaneous thrombosis may be dramatically different as shown in another of our cases.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

A man aged 25 was admitted to another hospital in February 1972 with very severe pain in the upper right abdomen and vomiting. He gave a history of flatulent dyspepsia for several months previously and at the age of 13 he had been investigated for a possible peptic ulcer. The upper right abdomen was acutely tender and rigid, he had moderate leucocytosis and a normal urine. A diagnosis was made of perforated peptic ulcer but laparotomy revealed no abnormality in the abdomen. He made an uneventful recovery. An intravenous pyelogram in the postoperative period showed a normal left kidney but a non-functioning right kidney. A right retrograde pyelogram was normal. He was transferred to Jervis Street Hospital for further study and selective renal angiography demonstrated complete thrombosis of the right renal artery. At this stage he was completely well with a normal blood pressure but in June 1972, 4 months after the acute episode, his blood pressure began to rise slowly to 160/100 mm Hg. At this stage the right kidney was removed and the blood pressure returned to normal. Again histological study of the renal artery demonstrated no abnormality other than localised complete thrombosis.

Tse and Leberman (1972) reported a similar case presenting as an acute abdominal crisis but in their patient only a main division of the right renal artery was occluded. They suggest that the diagnosis of acute renal artery occlusion should be strongly suspected in a patient presenting an

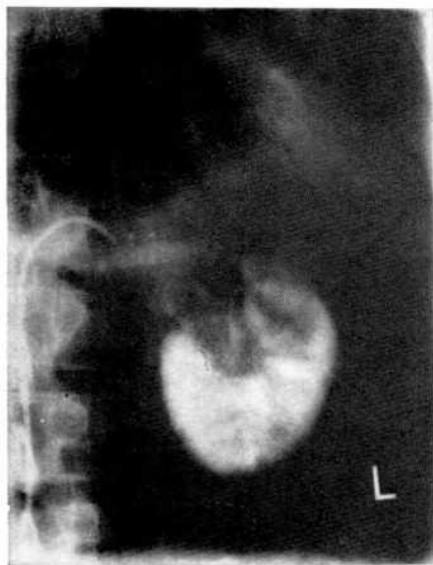


Fig. 1. The nephrogram phase of a selective renal arteriogram following traumatic infarction of the upper half of the kidney.

acute onset of severe loin and flank pain radiating to the front and associated with nausea and vomiting.

The lesson of these 2 cases of spontaneous thrombosis is that the condition may present either with hypertension and no other symptoms or as an acute abdominal crisis. In the traumatic cases it is obvious that the diagnosis must be made very early if the kidney is to be saved but it is worth noting that Morton and Crawford (1972) have reported the case of a 17-year-old man who suffered bilateral renal artery thrombosis following trauma. Revascularisation was not performed until 18 hours after the injury but there was eventual recovery of adequate renal function although the patient is hypertensive.

Summary

Renal artery thrombosis may follow blunt trauma or may be spontaneous. It causes hypertension that may be fulminant or very insidious in onset.

Spontaneous renal artery thrombosis may present as hypertension or as an acute abdominal crisis.

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The Fate of the Unoperated Staghorn Calculus

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One of the concepts in urology which dies most hard is that of the "silent staghorn calculus". When in 1949 Priestley and Dunn reviewed 382 cases of staghorn calculi from the Mayo Clinic, they pointed out how rarely was a staghorn calculus not accompanied by severe urinary symptoms, and they went on to show that even in pre-antibiotic days it was better to remove the stone than to do a nephrectomy, and better to do a nephrectomy than to do nothing. Despite this renewed interest in nephrolithotomy, urological units continued to regard the operation with suspicion, not least because of the high rate of secondary haemorrhage. Good results from the renal bivalve operation were the exception (Maddern, 1967).

Some 15 years later Gil-Vernet (1964) demonstrated how it was possible to remove large staghorn calculi without cutting into the renal parenchyma. Even this was received with a good deal of criticism. Some of the critics argued that, because staghorn calculi were generally silent, one would do better to leave them alone, usually supporting their arguments with anecdotes rather than with statistics. Others pointed out the stupidity of removing the stone if it was bound inevitably to recur. Nephrectomy seemed to them a far better way out.

We have always been enthusiasts for Gil-Vernet's operation (Blandy and Tresidder, 1967; Singh, Tresidder and Blandy, 1971) and have now removed more than 103 large staghorn calculi from 86 patients, 16 of them with bilateral calculi.

Our follow-up now extends to nearly 9 years and further experience since we reported our results 2 years ago (Singh *et al.*, 1971) has only tended to confirm our favourable impression; the results if anything have tended to improve as we have got better at it.

The questions however we have still not answered are:

1. Would not these patients have been just as well served if we had left them alone?

or

2. If we had just performed a nephrectomy?

Our critics have pointed out that they would not be likely to have done as badly as those in Priestley and Dunn's pre-antibiotic series, now that there are better means of controlling infection.

It was plainly not possible to compare identical groups of patients, because in the last 9 years virtually every new case referred with a staghorn calculus has been operated on. Nevertheless, we have thought it worthwhile to find out what really did happen to patients with staghorn calculi in a period when antibiotics were available, but Gil-Vernet's operation was not. We have called them "untreated", meaning untreated by extended pyelolithotomy, although they received every other form of therapy available at that time.

Composition of Series

We were able to find records of 54 patients seen at the London Hospital in the years 1955 to 1972 with a diagnosis of staghorn calculus (Table I). Nine of these had bilateral calculi, so that in all 63 kidneys were studied. Of the unilateral cases, 8 had smaller calculi in the other kidney. There

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were 40 females and 14 males (Table II). The mean age of untreated patients (56.4 years) however was somewhat higher than the treated ones (46.6 years).

Table I

Staghorn Calculi not Treated by Gil-Vernet Extended Pyelolithotomy. The London Hospital, 1955-1972.

	Patients	Kidneys
Unilateral	45	45
Bilateral	9	18
Total	54	63

Table II

Untreated Staghorn Calculi

Sex Incidence	
Males	14
Females	40
Total	54

Not-so-silent Stones

None of the patients was symptomless on admission. Most of them had pain, haematuria or infection, and many had all three (Table III). Unfortunately we had no way of knowing how

Table III

Untreated Staghorn Calculi—Symptoms

	Patients	%
Pain	44/54	81.5%
Haematuria	26/54	48.0%
Infection	43/54	79.4%

many other unsuspecting members of the public were walking around with silent calculi. But we could find out how many times unsuspected calculus would turn up at postmortem.

Over the same period, 8,996 postmortem examinations were performed at The London Hospital, among which staghorn calculi were found in 9 cases (Table IV). Only 4 of these cases had no

Table IV

Staghorn Calculi found Incidentally at Postmortem.
The London Hospital, 1959-72

Total No. of postmortems	8,996
No. of urinary tract lithiasis	59
Staghorn calculi without symptoms	4
Staghorn calculi with symptoms	5

severe or persistent symptoms during the patient's lifetime and in these 4 the renal parenchyma was reduced to a thin scarred shell. This would suggest that if silent stones do occur, then they are very rare indeed (0.05%).

Table V

Unilateral Staghorn Calculi (45 Patients)

	Patients	Subsequent Death	Survivals
Primary nephrectomy	20 (44.5%)	4	16
Delayed nephrectomy	12 (26.7%)	3	9
No surgical treatment	13 (28.8%)	9	4
Total	45 (100%)	16 (35.6%)	29 (64.4%)

Subsequent Fate of 54 "Untreated" Patients

Unilateral Staghorn Calculi (45 Patients) (Table V)

Nephrectomy was performed in the first instance in 20 of these patients, in 4 of them the other kidney continued to deteriorate and they died of renal failure. The remaining 16 are still being followed up. In 25 patients the stones were initially left alone: 12 of them subsequently had to have a nephrectomy, an event usually precipitated by pyonephrosis or intolerable symptoms and 3 of these patients subsequently died of uraemia.

Of the remaining 13, no less than 9 are known to have died, and so of the 16 patients known to have died, all but 4 died from renal failure.

This small series bears out Priestley and Dunn's suggestion that unilateral cases do better when treated by nephrectomy than when the stone is left *in situ*.

Table VI

Bilateral Staghorn Calculi (9 Patients)

	No.	Deaths	Survival
Expectant treatment	5 (56%)	4*	1
Subsequent nephrectomy	4 (44%)†	0	4
Total	9 (100%)	4 (44%)	5 (56%)

* All 4 died of renal failure at 17 years, 1 year, 2 years and 4 years respectively after initial diagnosis.

† Nephrectomy at 10, 8, 1 and 13 years respectively after initial diagnosis.

None of the 5 survivors is without chronic symptoms.

Bilateral Staghorn Calculi (9 Patients) (Table VI)

Four of these patients had to have a nephrectomy usually for pyonephrosis and all of them are still alive, but all have continuous and severe symptoms. Of the remaining 5, 4 have died and the only survivor with truly giant calculi is far from being well.

Discussion

One may summarise these findings quite shortly. Nearly half of these patients have died of progressive renal failure in the period of follow-up. Evidently staghorn calculi are neither silent nor

safe. Those who had a nephrectomy fared better than those in whom the stone was left *in situ*: it seems that leaving a stone *in situ* poses a constant threat to the other kidney, and also an ever-present risk of pyonephrosis. Expectant treatment, based on the idea that stones are silent and safe, leads to enforced nephrectomy in half the cases and to death in the majority of the others.

In comparison with these figures, the results of removing staghorn calculi are encouraging

Table VII

Fate of Staghorn Calculi Treated by Extended Pyelolithotomy. The London Hospital, 1964-73

Patients	No.	Subsequent nephrectomy	Subsequent death
Unilateral	70	2	2
Bilateral	16	1	3
Total	86	3	5

Period of follow-up extends to 6½ years and 41 patients have been followed up for more than 2 years.

(Table VII), although we admit that these patients have been followed up for far less time than have the untreated cases.

Only 5 out of 86 patients have died and of these 3 had advanced renal failure when first referred to us after prolonged observation elsewhere. 3 of the 103 kidneys have come to nephrectomy, but 2 of these had no demonstrable renal function when the stone was first removed and they should probably have had a nephrectomy in the first place.

Table VIII

Recurrence of Staghorn Calculi after Removal

	Kidneys	Recurrence	%
Complete removals	86	9/86	10.5
Incomplete removals	17	4/17	23.0
Total	103	13/103	12.6

As we have shown before, new stone formation is not the rule and occurs in less than 1 in 5 kidneys. (Table VIII).

The most striking feature is that these patients continue to be without pain or haematuria, and the incidence of urinary infection has fallen from around 80% to under 25%.

Conclusion

The concept of the "silent staghorn calculus" is a false one. Conservative treatment of a staghorn calculus should be early and complete removal of the stone.

Summary

A retrospective study has been carried out to study the fate of unoperated staghorn calculi.

54 patients (63 kidneys) have been studied over a period of 17 years and the outcome has been compared with a series of patients where staghorn calculi have been treated by extended pyelolithotomy.

The patients with staghorn calculi are rarely symptom-free unless they are operated on.

Expectant treatment of these cases has led to subsequent nephrectomy in half the cases and the majority of the rest have died of progressive renal failure.

By comparison patients treated surgically have fared significantly better.

The value of early and complete removal of staghorn calculi has been stressed.

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Factors Influencing the Survival of Patients with Transitional Cell Tumours of the Urinary Bladder

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In order to treat bladder neoplasm in a rational manner it is necessary to know those factors which influence the prognosis. *Tumours of the Bladder* (ed. Wallace, 1959) contains a wealth of statistical data. Further data may be found in the reports from Bristol (Miller, Mitchell and Brown, 1969) and the London Hospital (Dix *et al.*, 1970) although these do not contain details related to the depth of tumour invasion. More recently Poole-Wilson and Barnard, 1971 (clinical staging) and Pomerance, 1972 (pathological staging) have discussed the depth of invasion in relation to the survival of patients treated by cystectomy.

This paper attempts to provide some current data based on the U.I.C.C. classification for bladder tumours.

Patients

691 residents of the United Kingdom attended St Paul's Hospital, London for the treatment of transitional cell tumours of the urinary bladder during the 10-year period 1960-69. They were treated by 1 of 6 urological surgeons or their deputies. Many of the patients had been previously seen at other hospitals and radiotherapy, when indicated, was given at 1 of 3 different centres. The factor common to all these patients was the pathological studies carried out in one urological pathology department.

This retrospective study was commenced in July 1972 and at the time of follow-up 311 patients were still alive and 356 patients had died. The ultimate fate of 24 (3.5%) patients was unknown but the clinical status of 10 of these patients 3 years after their initial treatment was known. The patients who were lost to follow-up were considered to have died (but not of tumour). The 7 operative deaths (4 after "open" operations and 3 after cystectomy) were considered to be the result of tumour.

Results

Four patients were found to have true papillomas of the bladder which were treated by endoscopic destruction. Each of these patients has remained well with no recurrence of the disease for 3-12 years. One patient was found to have carcinoma *in situ*, and after much hesitation—2 years after initial presentation—a cystectomy was performed. He remained free of carcinoma but died 4 years later probably from complications from his ileal conduit.

The remaining 686 patients had transitional cell carcinomas of the urinary bladder and the survival of these will be discussed in greater detail.

1. Depth of Invasion

(a) Clinical Assessment

It was possible to assess the stage of 627 patients from the notes and this showed the crude 3-year survival rate to be 82% if the tumour was confined to the mucosa (T1), 48% when the superficial

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muscle was invaded (T2) 21% when there was deep muscle invasion (T3) and only 4% when there was invasion of other pelvic organs (T4). This data is shown more fully in Table I and analysis shows that there was a statistically different survival rate in the 4 groups ($P < 0.001$).

During the subsequent 7 years a further 43 (10%) of the 3-year survivors died of bladder cancer. There was no statistical difference in the subsequent deaths due to tumour in each of the 3 clinical stages (T₁, T₂, T₃).

Table I

Three-Year Survival of Patients Related to the Clinical Assessment of Tumour Invasion

Depth of Invasion	Number of Patients			Total	Subsequent Deaths of Tumour
	Alive	Dead of Disease	Dead of Other Causes		
Mucosal (T1)	348 (82%)	34	46	428	32 (9%)
Superficial muscle (T2)	40 (48%)	35	8	83	7 (17%)
Deep muscle (T3)	19 (21%)	63	8	90	2 (10%)
"Pelvic fixation" (T4)	1 (4%)	23	2	26	...
Unknown	26	21	12	59	2 (8%)
χ^2 (T ₁ -T ₄)	> 100	> 100	0.49	...	2.63
Significance	$P < 0.001$	$P < 0.001$	None	...	None

Table II

Three-Year Survival of Patients Related to Combined Clinical and Pathological Evidence of Invasion

Stage	Number of Patients			Total	Subsequent Deaths due to Tumour
	Alive	Dead of Disease	Dead of Other Causes		
I-S	157 (88%)	6	15	178	6 (4%)
1a	64 (77%)	8	11	83	8 (12%)
1b	53 (64%)	20	10	83	10 (17%)
2	30 (52%)	28	0	58	5 (20%)
3	27 (24%)	74	18	119	2 (10%)
4	0	31	1	32	...
T1 P?	98 (80%)	6	17	121	12 (12%)
T? P?	6 (42%)	3	3	12	...
χ^2 (1S-4)	> 100	> 100	13.98	...	13.96
Significance	$P \leq 0.001$	$P \leq 0.001$	$0.02 > P < 0.01$	...	$0.02 > P < 0.01$

(b) Pathological Evidence of Tumour Spread

The above clinical staging may be revised in the light of the pathological findings and the revised survival data are shown in Table II. Once again the relationship between the extent of invasion and the patient survival is highly significant ($P < 0.001$). Pathological material was not available in 133 patients but of these 121 patients had T1 tumours (110 being treated endoscopically) and the results were similar to those patients where the tumour was not invasive.

The pathological data in Table II is not homogeneous as in many patients only biopsy material was available for examination. In these patients the degree of invasion is taken on the combined results of the clinical and histological evidence. In order to give more precise survival data, based on the histological evidence of the depth of invasion, the survival rates were calculated for those patients treated by open excision of the tumour or cystectomy. Table III shows that the results for this group of patients do not differ significantly from the larger group—even for those tumours with superficial muscle invasion.

Table III

Three-Year Survival Related to the Pathological Evidence of the Depth of Invasion

Stage	Number of Patients			Total
	Alive	Dead of Disease	Dead of Other Causes	
PIS	50 (85%)	5	4	59
P1a	36 (72%)	7	7	50
P1b	32 (64%)	12	6	50
P2	24 (62%)	15	...	39
P3	20 (27%)	42	13	75
P4	0	8	...	8
χ^2	86.4	56.9	10.32	...
Significance	P < 0.001	< 0.001	None	...

Table IV

Three-Year Survival Related to the Tumour Morphology

Morphology	Number of Patients			Total
	Alive	Dead of Tumour	Dead of Other Causes	
Papillary—differentiated	83 (81%)	11	8	102*
intermediate	4	1	0	5
anaplastic	1	2	1	4
Papillary—differentiated	18 (62%)	6	5	29*
and solid intermediate	18 (58%)	7	6	31*
anaplastic	18 (44%)	14	9	41*
Solid—differentiated	1	1	1	3
intermediate	4	9	1	14
anaplastic	11 (22%)	34	3	48*
χ^2 *	50.5	54.7	8.3	...
Significance	P < 0.001	P < 0.001	None	...

* Calculated on the 5 large groups.

Only 9 patients were known to have lymph node invasion at the time of the initial treatment and 7 of these died rapidly of tumour. The 2 patients who survived had solid tumours (1 of intermediate grade, 1 anaplastic) invading the deep muscle and were treated by partial cystectomy and subsequent irradiation. Both patients remained free of disease and 1 was alive 12 years later; the other died of myocardial infarction 9 years after treatment.

II. Tumour Grade

Table IV shows that there is a highly significant difference in the 3-year survival rates occurring in relationship to the tumour morphology. The survival data in this table relates to those patients treated by open excision or cystectomy and are calculated irrespective of the extent of tumour invasion. The degree of tumour differentiation correlates closely with the extent of invasion as can be seen in Table V.

III. Age and Resistance of the Patient

There was a significant increase in proportion of tumours invading muscle in the older age groups (Table VI, $P < 0.01$) but there was no difference in the survival and "death from disease" rates

Table V

The Relationship Between Tumour Morphology and Depth of Invasion

Tumour Morphology	Tumour Stage			Total
	PIS	P1a and P1b	P2, P3, P4	
Papillary—differentiated	58 (57%)	42	2	102
Papillary—differentiated		16	13	29
and solid intermediate		14	17	31
anaplastic		9	32	41
Solid—anaplastic		7	41 (86%)	48

Table VI

The Relationship between the Incidence of Muscle Invasion and the Age of the Patient

Muscle Invasion	Age (years)						Total
	< 40	40-49	50-59	60-69	70-79	> 80	
Absent	17	39	117	173	100	19	465
Present*	2	10	54	75	59	21	221
$\chi^2 = 17.25$							$P < 0.01$

* Includes 12 patients T? P?

in each stage for patients of different ages. As would be expected there was a significantly greater number of deaths from "other causes" in the older age groups ($\chi^2 = 36.6$, $P < 0.001$).

The equality of the sexes was maintained and the 126 women were distributed throughout all stages of the disease and survived equally well.

IV. The Effect of Treatment

Table VII summarises the various methods of initial treatment selected by each of the 6 surgeons. Each surgeon's psychological attitude towards bladder tumours is reflected in his choice of treatment regime. Some surgeons followed the conventional methods of treatment (CDE) whilst others reflect a more conservative approach (F). Two surgeons (AB) placed great reliance upon the open excision of the tumour combined with interstitial irradiation. These differences in treatment are not due to differences in the tumour stages (Table VIII), and despite these wide variations

in treatment there was no statistical difference in the survival or death rates in any stage for the different surgeons (Table IX).

Much interest centres around the best treatment for those tumours that are invading deep muscle. Table X shows the methods of treatment chosen by the different surgeons and the wide variations in the results obtained. Excellent results (35% and 37% 3-year survival) were obtained without or with the use of cystectomy respectively. Unfortunately there was no significant difference in the results obtained as a whole.

Table VII

The Initial Treatment Regime at St Paul's Hospital Selected by Each Surgeon

Surgeon	Endoscopic	Open Excision ± Interstitial Irradiation	Cystectomy ± DXT	Radiotherapy	Total
A	49 (34%)	82 (56%)	1	11 (8%)	145
B	42 (37%)	67 (58%)	1	1	115
C	65 (43%)	59 (39%)	4 (3%)	20 (13%)	151
D	26 (51%)	10 (20%)	5 (10%)	8 (16%)	51
E	67 (55%)	32 (27%)	7 (6%)	12 (10%)	121
F	58 (56%)	17 (17%)	4 (4%)	18 (18%)	103
χ^2	30.18	72.5	...	21.23	686
Significance	P < 0.001	P < 0.001	...	P < 0.01	...

Table VIII

Depth of Invasion in Each Surgeon's Series

Surgeon	% in Each Stage		
	None	Submucosal Invasion	Muscle Invasion
A	38	26	34
B	39	22	35
C	43	23	30
D	49	24	27
E	48	29	23
F	45	23	32
χ^2*	5.05	2.23	6.57
Significance	None	None	None

* Calculations on actual numbers.

Discussion

Although many of the factors shown to be influencing the survival of the patients are generally accepted, there is little statistical confirmation of this in relation to the U.I.C.C. classification of the extent of bladder tumours. Most papers concerned with the treatment of bladder tumours report the results of a particular method of treatment, but without the use of a closely controlled clinical trial. It is probable that the improvements obtained are the result of chance, different methods of patient selection, and a general decrease in other causes of death. In this series it was

assumed that any consistent errors of mis-staging by a given surgeon would be apparent in the overall results. This may have occurred to some extent as the surgeons with the best results for tumour invading deep muscle (A and D) had the worst results for invasive tumours not involving muscle (1a and 1b). The precise meaning of this is uncertain as there was histological evidence of deep muscle invasion in 90% of the patients.

Table IX

Percentage of 3-year Survivors for Each Surgeon with Regard to the Depth of Invasion

Surgeon	Stage						
	T1 P?	I-S	1a†	1b†	2†	3†	4
A	87	76	69	44	60	35	0
B	73	100	83	65	60	13	0
C	82	88	78	86	57	16	0
D	68	78	71	60	50	37	0
E	84	86	80	65	17	13	0
F	86	57	82	68	44	27	0
χ^2*	3.84	10.47	1.30	4.33	3.38	5.86	0
Significance	None	None	None	None	None	None	...

* Based on actual numbers.

† Groups combined, e.g. best 2 results, worst 2 results and remaining pair.

Table X

Surgeon's Choice of Treatment for Tumours Invading Deep Muscle and the Percentage of Patients Surviving 3 Years

Surgeon	Treatment (Number of Patients)				Pathological Evidence of Deep Muscle Invasion	Total Number of Patients	3-year Survival
	Endoscopic	Open Excision	Cystectomy	Radiotherapy			
A	...	25 (81%)	...	6	28	31	11 (35%)
B	1	27 (87%)	1	2	28	31	4 (13%)
C	...	8	3	7	12	19	3 (16%)
D	...	1	3	4 (50%)	5	8	3 (37%)
E	1	6 (80%)	3	5	11	15	2 (13%)
F	...	1	4	10 (67%)	8	15	4 (27%)
						χ^2*	5.86
						Significance	None

* Groups combined in pairs.

The survival of patients with tumours involving the deep muscle is of interest in that the 2 surgeons (A and D) who obtained good results used widely differing methods of treatment and the 2 surgeons who used similar methods of treatment (A and B) obtained dissimilar results. Despite the wide variations in results, the probability remains that the variation was due to chance. This illustrates the need for applying simple statistical tests. In general it might be added that when statistics are required to show the difference between 2 groups it is unlikely to be of any clinical importance.

What conclusions may be drawn from this study? The results emphasise that the most important factor in the survival of the patient is the nature and stage of the tumour. As all the treatment regimes seem to be equally effective the simplest method of eliminating each tumour should be selected.

Summary

The prognosis in transitional cell carcinomas of the bladder may be assessed by the: (1) clinical assessment of the depth of invasion; (2) pathological evidence of the depth of tumour invasion; (3) the degree of tumour differentiation; (4) the absence of lymph node invasion; (5) the patients age—older patients are more likely to have tumours invading muscle.

The choice of surgeon and the treatment regime used did not influence the prognosis.

I would like to thank the surgeons at St Paul's Hospital for their help and also Dr R. C. B. Pugh for his help. I would also like to thank Miss Mona O'Connor for her invaluable assistance, as without her help it would have been impossible to achieve a 98% complete 3-year follow-up.

This work was carried out at St Paul's Hospital and the Institute of Urology.

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Evaluation of Helmstein's Distension Method for Carcinoma of the Bladder

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In 1966 Helmstein described a new method for treating vesical cancer by distending a balloon inside the bladder, the purpose being to reduce blood flow and cause tumour anoxia with subsequent necrosis. The results he reported at Leeds in 1971 were remarkably good particularly in deeply invasive anaplastic tumours, and he considered that these tumours were the most important indication for using his technique. He suggested too that distension may work in part by stimulating some immunological defence mechanism.

Whatever the explanation, the results he reported were too good to be ignored and we began a clinical trial on selected patients at The London Hospital and at St Peter's Hospital.

Table 1

Patients—Tumour Stage, Gross Pathology and Histology

Stage	Gross Pathology	Histology	Totals
T1	Long fronded loose papillary—multiple single	Pap. diff.	{ 11 2
		multiple	
	Short fronded compact papillary—multiple	Pap. diff.	7
	Flat red plaque	Pap. intermed. (<i>in situ</i>)	1
	Solid	Pap. and solid anaplastic	2 24
	T2	Solid	Sold diff.
Pap. and solid intermed.			1
Solid anaplastic			1 3
T3	Solid	Pap. and solid intermed.	2
		Solid anaplastic	6 8
T4	Solid	Solid diff.	1
		Solid intermed.	3
		Solid anaplastic	5
		Squamous	2 11
Total			46

Material

49 patients have been treated and followed up at least once and form the basis of this report. They include 37 men and 12 women with ages ranging from 46 to 87 years. 46 had carcinomas and 3 were bleeding from post-radiation necrosis.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

All tumours had preoperative cystoscopy, bimanual assessment of clinical stage, and biopsy. This was repeated 6 weeks after distension and subsequently at intervals of 6 to 12 weeks. Tumour staging and grading conformed to the Institute of Urology standard system (Wallace, 1959). Tumour stages, gross pathology and histology are summarised in Table 1.

Of the 24 T1 cases, 21 had papillary tumour and in 19 of these the growths were multiple, involving large areas of the bladder. The papillary tumours were sharply divided on gross pathological appearance into 2 groups—long fronded loosely arranged tumours—14 cases; and short fronded compact tumour—7 cases (Fig 1). One flat carcinoma-in-situ and 2 solid anaplastic carcinomas completed the group.

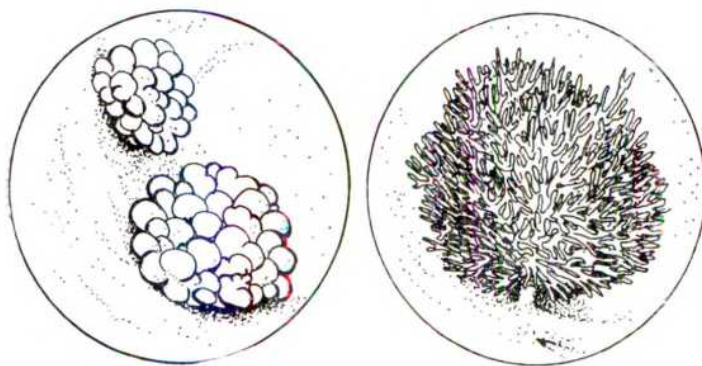


Fig. 1. The two forms of superficial (T1) papillary tumours: the "raspberry" form with short compact fronds responds poorly to distension therapy. The "seaweed" form with long loose fronds responds very well.

The T2-T3 categories included 11 patients who together with the T1 group made a total of 35 in whom cure was apparently possible.

There were also 11 T4 patients and for these only palliation could be expected. 22 patients had differentiated tumours and 24 had intermediate or anaplastic growths, anaplasia being the rule in the deeply invasive tumours.

In 9 patients the major problem was uncontrollable bleeding, 6 from tumour and 3 from post-radiation necrosis.

Immunology

In 11 cases lymphocytes from the patient were tested for their responsiveness to phytohaemagglutinin and for their cytotoxic activity against a standard culture of human bladder papillary carcinoma.

Technique

One of us (H. R. E.) had the privilege of studying Helmstein's technique at first hand and this was followed exactly (Helmstein, 1972), except that instead of a toy balloon we used a specially designed latex balloon made to our requirements. Where possible the balloon was distended for 6 hours at a pressure of at least 10 mm mercury above the diastolic blood pressure.

Complications

There was 1 death attributable to the treatment in a man having an emergency distension for severe bleeding. He was in heart failure and during the operation had an extension of a recent myocardial infarct and died after 5 days. One T4 patient with a small capacity bladder became incontinent due to the balloon being distended partly in the prostatic urethra. The 1 ruptured bladder settled uneventfully on catheter drainage and there were 4 cases of infection who all settled quickly with treatment.

Results

Results have been classified as "total necrosis" when the bladder was completely cleared, "substantial necrosis" if a majority of tumour was eliminated and "no improvement" in the remainder; details are shown in Table 2.

Table II
Results by Stage, Gross Pathology and Histology

Stage	Gross Pathology	Histology	Total Necrosis	Substantial Necrosis	No Improvement	Totals
T1	Long fronded loose papillary	Pap. diff.	4	8	...	12
		Pap. intermed.	1	...	...	1
	Short fronded compact papillary	Pap. Diff.	...	2	5	7
	Flat red plaque	Pap. intermed. (<i>in situ</i>)	1	...	...	1
	Solid	Pap. and solid anaplastic	...	...	2	2 23
T2	Solid	Solid diff.	...	...	1	1
		Pap. and solid intermed.	...	...	1	1
		Solid anaplastic	1	...	...	1 3
T3	Solid	Pap. and solid intermed.	...	1	1	2
		Solid anaplastic	...	...	6	6 8
T4	Solid	Solid diff.	...	1	...	1
		Pap. and solid intermed.	...	2	1	3
		Solid anaplastic	...	2	3	5
		Squamous	...	...	2	2 11
			7	16	22	45

Response of Tumour

One particular type of T1 tumour—the long fronded loose papillary—responded uniformly well, 5 being completely cleared, whilst in the other 8 only tiny areas of tumour remained (Fig. 2). The results were quite different with the stubby fronded compact tumours of the same histology, only 2 of 7 showing limited improvement (Fig. 3). The 2 anaplastic T1 carcinomas were failures, but the flat carcinoma-in-situ was clear at follow-up, despite a distension limited to 2 hours because of bladder rupture.

When the tumour was solid and infiltrating (T2-T3), only 1 case responded satisfactorily. This was a very disappointing result, particularly as these were the tumours in which Helmstein had reported such good results and which he considered to be the main indication for distension therapy.

Five of the 11 T4 patients gained substantial benefit from control of bleeding and increase in bladder capacity following necrosis of some intra-luminal tumour.

Subsequent Course of Bladders Cleared of Tumour

Of the 6 T1 patients, 1 remains clear after 6 months, 1 had no recurrence at cystectomy for bleeding after 4 months, and the other 4 cases developed new tumour after 12, 9, 3 and 2½ months respectively. The 1 T2 patient was clear of his tumour high on the lateral wall at 5 months, when he was given radiotherapy for transitional cell carcinoma in the prostate.

Effect on Bleeding

All 9 cases with dangerous haemorrhage were controlled immediately. Of the 6 bleeding from tumour, 2 had no further bleeding in 6 months, 1 died after 4 months without recurrence, 2 had successful second distensions at 6 and 8 months and 1 had a cystectomy for renewed bleeding

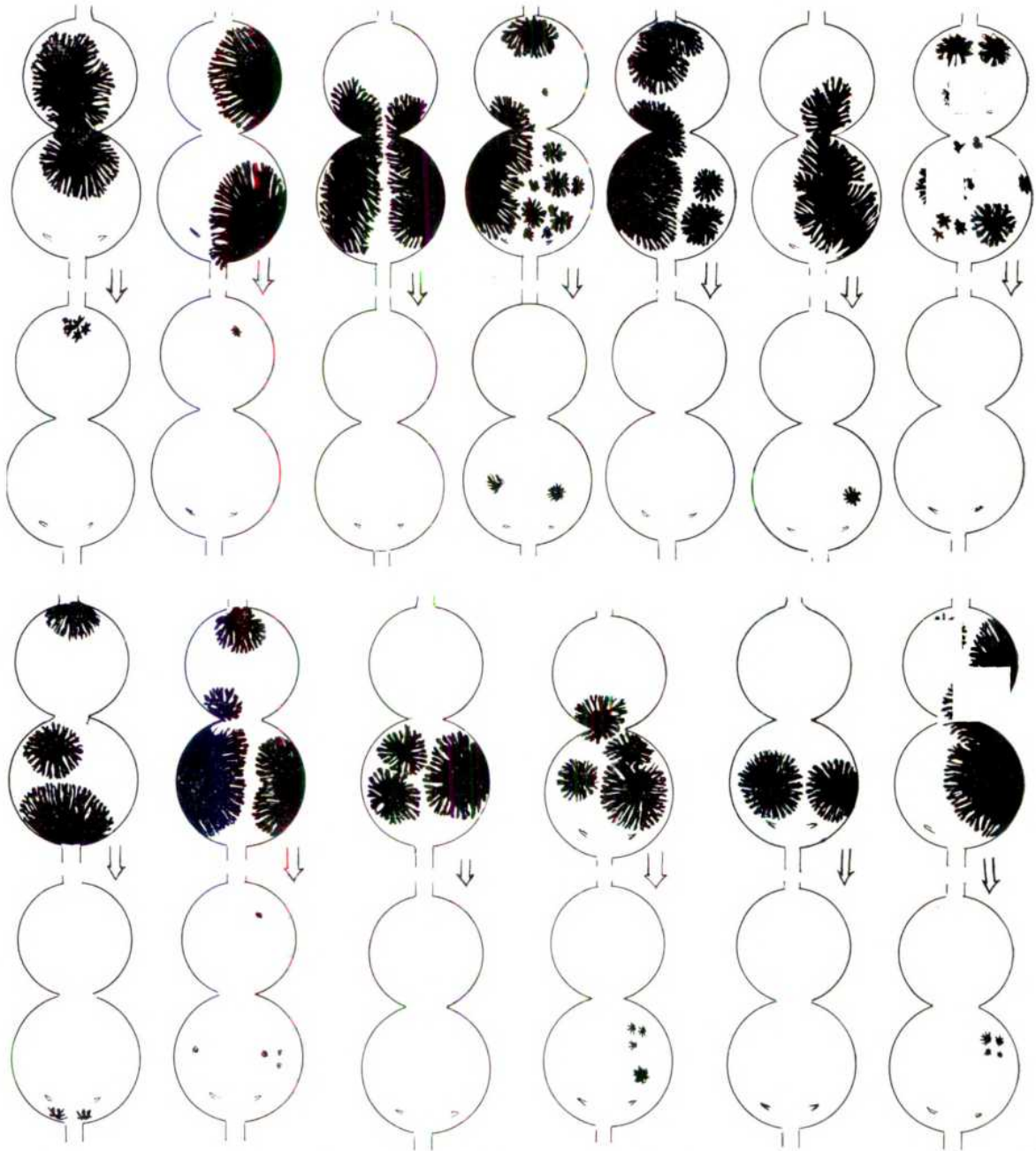


Fig. 2. The response of the long loose fronded T1 papillary tumours based on drawings made at the time of pre- and post-operative cystoscopy.

after 4 months. Two patients were in T1, 1 in T3 and 3 in T4 groups respectively, so response was independent of stage, grading or gross pathology, and as was discovered at follow-up, independent of whether or not there had been tumour necrosis.

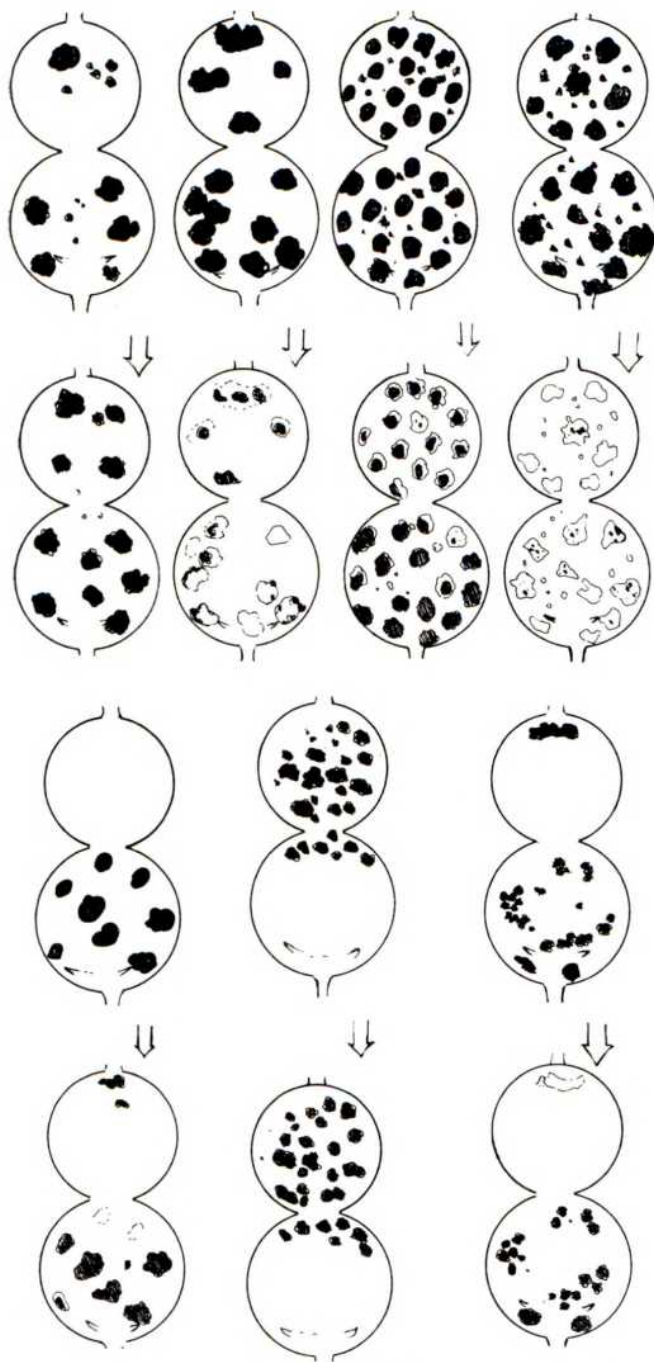


Fig. 3. The response of the short fronded compact T1 papillary tumours based on drawings made at pre- and post-operative cystoscopy.

The successful results in all 3 patients bleeding from post-radiation necrosis were even more gratifying because cystectomy would have been the only reliable alternative. There has been no recurrence of haematuria and as I has been free now for over 15 months, the effect seems to be a lasting one.

The ability of distension to control bleeding may well be its most important contribution.

Discussion

Only one type of tumour responded well—the long fronded loosely arranged T1 papillary (Fig. 4). The stubby fronded compact tumours of similar histology showed limited or no response, as did the T1 solid anaplastic carcinomas.

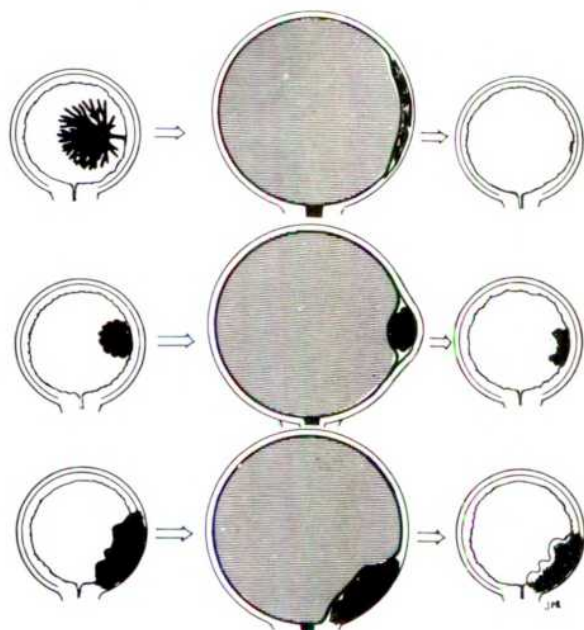


Fig. 4. The response is dependent upon the gross physical character of the tumour. The only tumour which responds uniformly well is the long and loose fronded T1 papillary carcinoma.

In the solid infiltrating tumours, except for the 1 success, any necrosis was confined to intraluminal growth leaving the deep infiltrating portion untouched.

The one feature which appeared to decide the outcome was the gross physical character of the tumour. If the tumour had any degree of substance, even as little as the stubby fronded compact T1 papillary type, it seemed able to resist devascularisation successfully.

Support for this observation, particularly in the case of infiltrating tumours, comes from the work of Mehrotra (1953), whose studies into the effect of distension on vesical circulation in the rat really form the background to the rationale of distension therapy.

He showed that blood flow was increasingly diminished as intravesical pressure was raised until eventually only intermittent flow was seen in some vessels of the outer coat. Vessels in the inner layers suffered most, being compressed between intravesical fluid and over-stretched muscle, but vessels in the outer coat were protected to some extent by the muscle fibres. If the bladder could not over-distend, a much greater pressure was needed to produce vascular occlusion.

The factors which resisted vascular obstruction in Mehrotra's experiments are all operating in the T2-T3 tumours, probably to an enhanced degree, and could explain the poor response. (1) Most of the tumour circulation comes from outer coat vessels, the most difficult to obliterate.

(2) Solid tumour shields the deep circulation, probably much more effectively than the muscle layer was shown to do. (3) Bladder wall involved by tumour is rigid and therefore cannot over-distend, making vascular obstruction more difficult.

Immunology

In the group investigated, no pattern of response has emerged and no conclusion can be drawn as yet.

Conclusions

Our experience with distension therapy suggests the following conclusions:

The technique is easy to perform and has few complications.

It can be relied upon to eliminate long fronded loose papillary tumour, but is of very limited value in short fronded compact tumour of virtually the same histology.

It cannot be recommended as treatment for T2-T3 tumours.

It may be of value in flat carcinoma-in-situ.

About one half of T4 tumours gain worthwhile palliation.

The effects of distension appear to be dependent on the gross pathology of the tumour.

It is an effective means of stopping bleeding from tumour or post-radiation necrosis.

Summary

Our experience with distension therapy in 46 cases of cancer and 3 of post-radiation haemorrhage has been presented. It is suggested that the procedure has a valuable though limited role to play in the treatment of bladder cancer, and that it is the best method available for controlling bleeding from tumour or post-radiation necrosis.

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The Stoma of the Ileal Conduit

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The most popular method of urinary diversion is the ileal conduit. Until a satisfactory bladder substitute or a better method of diversion is devised the ileal conduit will remain, for many surgeons, the operation of choice when a permanent method of urinary diversion is required. Instead of searching for other ways to divert the urine we have concentrated on this existing method of diversion to discover its defects and remedy them where possible. Although many factors may be responsible for the maintenance of renal function in patients with ileal conduits, this paper is concerned with only one, the stoma.

This paper describes what can be discovered from simple clinical inspection of the stoma and from measurements of its efficiency. It suggests the best method of construction and gives the indications for refashioning.

Patients and Procedures

55 patients with ileal conduits were studied. Urinary diversion had been carried out for the conditions shown in Table I. The most important difference in the operative technique was as

Table I

Conditions for which Ileal
Conduit was Performed

Carcinoma	33
Bladder	32
Cervix	1
Spina bifida	12
Neurogenic bladder	4
Ectopia vesicae	3
Others	3
	55

follows. In one group the stoma was constructed by the method described by Turnbull, Schofield and Hawk (1968). The stoma was of everted type and the mesentery of the last 5 cm of the ileal segment was ligated to prevent bowing of the stoma. These authors considered that after this procedure the blood supply to the stoma was still adequate. In a second group the stoma was constructed using a modification of the method described by Brooke (1954) and Goligher *et al.* (1968) (Fig. 1). The stoma was again of everted type, but the mesentery to the distal end of the ileal segment was preserved. This is the method of construction we use at present. The end of the ileum is brought out through the anterior abdominal wall to project approximately 6-8 cm. Fixation is achieved first by sutures joining the ileum to the subcutaneous fascia and secondly by sutures which pick up 3 points—the subcuticular layer of the cut skin edge, the seromuscular layer of the ileum and the full thickness of its cut margin; these sutures also effectively evert the stoma. Finally, the mucosa and skin are accurately apposed by a few additional sutures.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

All patients were studied in the morning out-patient clinic. As the study was a comparative one all the patients were examined supine, in a similar state of hydration and 2 hours after a light breakfast. The following facts were recorded:

The appearance of the stoma and its peristaltic activity was observed.

The efflux of the urine was collected in a perspex ring, which was fitted to the appliance, and measured. The mean of at least 6 measurements was taken as the efflux volume.

The periodicity of the efflux was recorded.

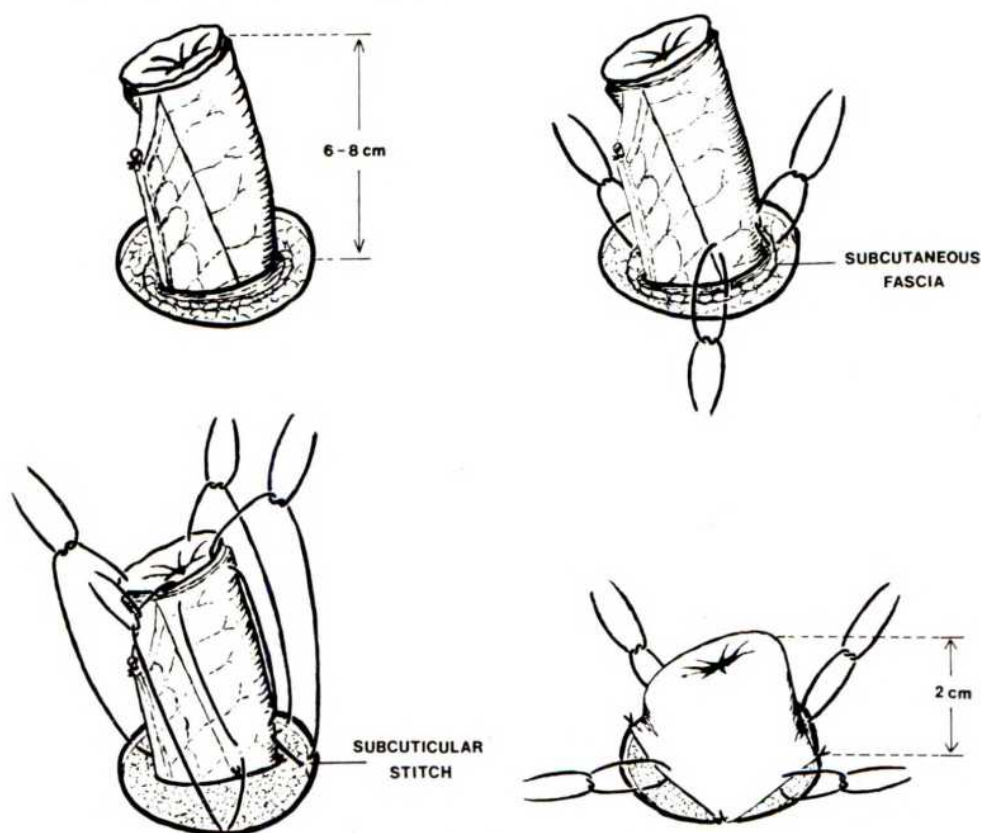


Fig. 1. Recommended method of constructing ileal stoma.

The residual urine was measured following an efflux by passing a sterile 5 Charrière catheter to the base of the conduit, aspirating it and continuing the aspiration as the catheter was slowly withdrawn. The greater trochanter was taken as the level of the base of the conduit.

The intraluminal pressure was measured using the same catheter connected to a transducer and recording apparatus (SE 4001 Amplifier and Recorder). The catheter was filled with water through a single-control tap system (Hepburn, 1971). This prevented blocking of the catheter with air or mucus and also allowed easy calibration of the transducer.

Results

Observation

The stoma was observed as to size, colour, type, evidence of keratinisation, mucus discharge and peristaltic activity.

42 stomas were found to be everted. These were of good colour and showed active peristalsis. There was no evidence of keratinisation in this group.

13 stomas were flat. The mucosa was darker and appeared less healthy than in the everted group and, in addition, peristaltic activity was less evident. 10 stomas showed keratinisation; this always began at the periphery. Eight had excessive mucus discharge and 2 had actual stenosis. Figure 2 shows the histological appearance. All of these complications occurred within the first year.

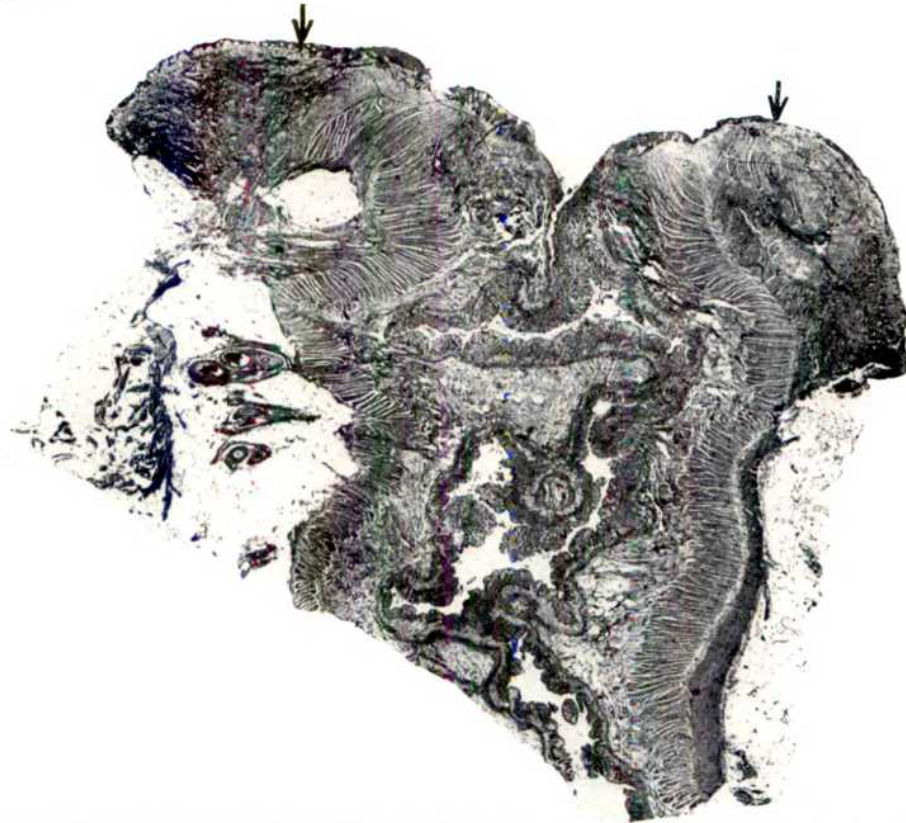


Fig. 2. Excised ileal stoma. The muscularis of the ileum is seen extending to the subcutaneous tissues. The orifice of the conduit is stenosed. Squamous epithelium extends from the mucocutaneous junction replacing the mucosa of the ileum between the arrows. H. and E. $\times 4.5$.

Efflux

With a healthy stoma urine is passed as an intermittent, forceful jet. This efflux can be initiated by any increase in abdominal pressure, for example coughing, sneezing or fitting the appliance.

Ingestion of food also makes the stoma much more active, proving that the gastro-ileal reflex is still present although the ileal segment is isolated. This effect of food on the activity of the ileal segment should always be borne in mind during measurements of its function.

Under the condition of study the volume of urine effluxed was in a remarkably narrow range, 1.4-6 ml, and in only 1 patient was it outside this range.

Periodicity of Efflux

This was also found to be in a narrow range, 2-10 minutes in all except 3 patients in whom it was more than 20 minutes. Two of these patients had large, dilated ureters before and after diversion and 1 patient had a keratinised stoma. The cause of the long interval between effluxes in these patients is unknown.

Residual Urine, Intraluminal Pressure and Renal Function

The volume of the residual urine was considered abnormally large if it was more than 20 ml, and the intraluminal pressure abnormally high if the basic pressure was more than 20 cm of water.

Deterioration in renal function was considered to have occurred if the pyelogram showed deterioration in any way when compared with the preoperative appearance, or if the blood urea rose outside the normal range of 20-40 mg/100 ml. If the preoperative blood urea was over 40 mg/100 ml, a rise of over 5 mg/100 ml was considered significant.

When the residual urine, intraluminal pressure and renal function were analysed, it was found that the series of 55 patients could be divided firstly according to whether the stoma was flat or everted, and secondly according to which of the 2 different operative techniques had been used.

Table II

Residual Urine, Intraluminal Pressure, Renal Function and Stomal Complications in Groups with Flat or Everted Stomas

Stoma	Cases	Residual Urine > 20 ml	Basic Pressure > 20 cm H ₂ O	Deterioration in Renal Function		Stomal Complications
				I.V.P.	Urea	
Flat	13	8 (61%)	10 (77%)	9 (69%)	10 (77%)	11 (85%)
Everted	42	5 (12%)	3 (7%)	4 (9%)	6 (14%)	1 (2%)

Table III

Residual Urine, Intraluminal Pressure, Renal Function and Stomal Complications in Groups with Mesentery Divided or Preserved.

Stoma	Cases	Residual Urine > 20 ml	Basic Pressure > 20 cm H ₂ O	Deterioration in Renal Function		Stomal Complications
				I.V.P.	Urea	
Everted mesentery divided	9	3 (33%)	4 (44%)	4 (44%)	4 (44%)	6 (66%)
Everted mesentery preserved	37	3 (8%)	4 (10%)	3 (8%)	6 (16%)	1 (2%)

Flat or Everted Stomas

Compared with the group with everted stomas, a greater proportion of the patients in the group with flat stomas had a large residual urine or a high intraluminal pressure. More also had deterioration in renal function or stomal complications.

Mesentery Divided or Preserved

Of the 55 patients 9 have been excluded. These 9 patients were operated upon before 1966; the majority had an extraperitoneal conduit, which Pekarovic, Robinson, Lister and Zachary (1968) have shown to be associated with an increased incidence of high intraluminal pressure and deterioration in the upper urinary tracts; in many the exact method of construction of the stoma was not known. In the remaining 46 patients the only difference in operative technique was in the construction of the stoma; in 9 patients the mesentery was divided and in 37 it was preserved.

Compared with the group which had the mesentery preserved, a greater proportion of the

patients in the group which had the mesentery divided had a large residual urine, high intraluminal pressure, deterioration in renal function and stomal complications.

Discussion

Measurement of the efflux volume and its periodicity was found to be of little clinical value, except that those patients with a long interval between effluxes had a large residual urine.

There is still controversy whether a flat or an everted stoma is better. The stoma originally described by Bricker (1950) was flat, the mucosa being accurately sutured to the skin. This type of stoma is still preferred by some surgeons, for example Malek, Burke and DeWeerd (1971). These authors reported, however, a 30% incidence of stomal problems. Others, for example Johnston and Rickham (1958), prefer an everted type of stoma and consider it to be less liable to complications. Our results support this view. Patients themselves prefer an everted stoma because the appliance is easier to manage.

Why are stomal complications so common? The reported incidence ranges from 15% to 43% (Pekarovic *et al.*, 1968). Three facts lead us to suggest that in the majority of instances stomal complications are caused by a deficient blood supply to the stoma. First, they have all occurred within the first year; second, they are also seen if the conduit has been fashioned from ileum thickened by previous radiotherapy; third, the unfortunate experience we have had with stomas constructed after division of the mesentery. We suggest that with everted stomas the sequence of events leading to stenosis is as follows: the blood supply is deficient, keratinisation occurs, the stoma becomes flat, stenosis follows.

We believe that a healthy looking, pink stoma which shows active peristalsis is a reliable sign of a healthy and active conduit. Conversely, we believe that keratinisation is a reliable sign of impending stenosis. Keratinisation or stenosis may produce higher pressures than normal within the conduit, reversing the normal pressure gradient, interfering with uretero-ileal drainage and leading to renal deterioration.

Therefore, we suggest the following policy: the ileal conduit should be an everted one and every effort should be made to preserve the best possible blood supply. Inspection of the stoma must be an essential part of the follow-up attendance of these patients. If keratinisation of the stoma is observed the stoma should be refashioned forthwith and especially if there is the slightest evidence that renal deterioration has occurred.

Summary

55 patients with ileal conduits have been studied. The stoma was carefully inspected, the interval between effluxes was timed and the volume of each recorded. The volume of residual urine and the pressure in the conduit were measured.

These findings have been correlated with the incidence of stomal complications and deterioration in renal function, as judged by changes in the pyelogram and blood urea level.

Because of differences between the groups with flat and everted stomas and between the groups with the mesentery to the stoma divided and preserved, we recommend that the stoma should be everted and its blood supply should be protected carefully. We suggest that the majority of stomal complications are caused by a poor blood supply to the stoma and this should be suspected if keratinisation is seen. We recommend that the stoma should be inspected at regular intervals and should be refashioned if keratinisation occurs.

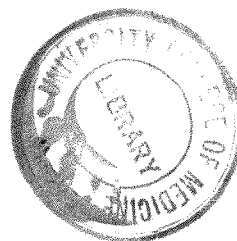
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Urological Complications of Cyclophosphamide

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Cyclophosphamide is a well known and well established drug used throughout the world as a cytotoxic agent. Reports of the urological complications associated with its use are becoming increasingly common. Any part of the urinary tract may be affected, but by far the commonest condition is cystitis, with or without haemorrhage. Three such cases are reported.

Case 1. A 62-year-old man presented in 1970 with symptoms of a lumbar disc prolapse which settled with rest and analgesics. In July 1972 he complained of general malaise with backache and headache. He had a haemoglobin of 8.7 g % and an E.S.R. of 136 mm in the first hour. X-rays of the spine showed collapse of the body of L5. A clinical diagnosis of myeloma was suspected and proven on bone marrow examination.

Cyclophosphamide 50 mg b.d. was started. Three months later, having received 8.4 g, he complained of extreme urgency and precipitancy of micturition. A catheter became necessary for the relief of symptoms and the drug was withdrawn. After 10 days the catheter was removed and there were no further urinary symptoms. Melphalan was substituted for cyclophosphamide and the patient is now well.

Case 2. A 57-year-old woman noticed a painful swelling of the outer end of the left clavicle in February 1966. She did not consult her doctor until August 1966 when an X-ray showed a trabeculated osteolytic tumour thought to be an osteoclastoma. No other bony lesions were discovered.

The tumour was explored and resected and histology showed it to be a plasmacytoma. She was referred for radiotherapy and received 4,000 rads.

She remained well for a year but in 1968 complained of persistent pain in the region of the remnant of the left clavicle. She was started on melphalan. In September 1968 she noticed a limp and further X-rays showed extensive disease throughout the pelvis, upper femoral shafts and chest. The melphalan was stopped because of leucopenia and cyclophosphamide 50 mg b.d. was started a month later.

One year afterwards she had improved remarkably and could walk up to 5 miles. Two and a half years later, in May 1971, she noticed marked painless haematuria. The cyclophosphamide was stopped: she had received 80 g. The bleeding subsided over a period of 6 weeks. Cyclophosphamide was restarted 6 months later because other drugs had failed to control her symptoms and there was evidence of further deposits. 15 months later, in February 1973, she again produced painless haematuria. The cyclophosphamide was withdrawn but it was 2 months before the bleeding stopped completely. It has not subsequently recurred.

Case 3. A 35-year-old woman developed painless haematuria in February 1972. She had been diagnosed as having Hodgkin's disease, proven histologically, in 1963 and received a total of 170 g of cyclophosphamide over a period of 9 years.

Physical examination revealed anaemia and a small gland in the left supraclavicular fossa. The urine was sterile and an I.V.P. was normal. The anaemia was corrected by blood transfusion and cystoscopy revealed marked generalised telangiectasia of the bladder mucosa with clear urine issuing from both ureteric orifices. No bladder tumour was observed. The cyclophosphamide was withdrawn.

The haematuria diminished during the following week but did not stop completely. One month later the palpable left supraclavicular gland was biopsied and the histology confirmed the previous diagnosis. Shortly after this the haematuria became profuse until clot retention occurred necessitating cystoscopic evacuation of the bladder under general anaesthetic. At this time the bladder was seen to be grossly haemorrhagic and oedematous, neither ureteric orifice could be identified, but again no tumour was seen. 400 ml of 2% formalin were instilled into the bladder for 15 minutes in an attempt to staunch the bleeding, but it was decided then that cystectomy would be necessary if the bleeding continued. The formalin reduced the haematuria and energetic blood replacement over the next 48 hours improved the patient's general condition so that a simple cystectomy with an ileal conduit could be performed. In all, 26 pints of blood were transfused during the 2 weeks prior to operation. Histology of the bladder revealed a grossly haemorrhagic mucosa with oedema and marked fibrosis of the bladder wall. No tumours were found.

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The patient made an uneventful recovery from the operation and 2 weeks later lymphangiography was carried out which revealed no abnormality. She has subsequently received a course of supervoltage radiotherapy to the "mantle" area and is now well.

Comment

Cyclophosphamide is an alkylating agent: it is the cyclic phosphamide of nitrogen mustard and is a well established and widely prescribed cytotoxic drug which has been in use since 1957. It is unusual in that the drug itself has no cytotoxic effect, but is converted into its unidentified active principles by tissues containing phosphamidase and phosphatase, predominantly the liver (Foley, Friedman and Drolet, 1961). Interestingly, phosphamidase activity has been shown by histochemical methods to be present in the superficial cells of the urothelium of the rat bladder (Meyer and Weinmann, 1957). Cyclophosphamide is excreted as Nor-N-mustard and N₂ chlor-ethyl aziridine (Brock and Hohorst, 1967), and 70% is cleared in the urine within 72 hours of administration (Bolt *et al.*, 1961). It is most commonly used in the treatment of lymphoproliferative disorders, but more recently has been found effective in other conditions such as the nephrotic syndrome, systemic lupus erythematosus and rheumatoid arthritis. It can be administered both orally and intravenously and the side effects of nausea, vomiting, diarrhoea, alopecia, leucopenia and hepatitis are well known. Less well known are the urological complications.

Philips *et al.* (1961) showed that the breakdown products of cyclophosphamide were responsible for the changes in the bladder mucosa, not the parent compound. Urine from dogs given cyclophosphamide was instilled into the bladders of dogs not on the drug: pathological changes were observed in the urothelium which did not occur when cyclophosphamide itself was introduced directly into the bladder. These changes therefore seem to be due to surface contact of the excretion products of cyclophosphamide and although the whole urothelium may be affected it is the bladder, where there is most stasis, that shows the most striking changes. Forni (Forni, Koss and Geller, 1964) showed the nature of the mucosal damage to resemble that seen after irradiation, the predominant feature being uneven cellular enlargement with irregular hyperchromatic nuclei. In the same study the urinary sediments of 26 patients taking cyclophosphamide were examined and all showed some changes. In 4 patients who developed haemorrhagic cystitis the cytology was grossly abnormal.

The vesical changes associated with haemorrhagic cystitis during cyclophosphamide therapy have become well documented in recent years. Goldman and Warner (1970) examined the bladder of a patient on cyclophosphamide suffering from haemorrhagic cystitis and found cytomegalic inclusion bodies in the transitional epithelium with ulceration and congestion of the capillaries in the lamina propria. Johnson and Meadows (1971) examined the bladders of 40 patients who had been on this drug and found that 10 showed fibrosis, 3 with telangiectasia, and that in this group of 10 patients 5 had had macroscopic haematuria. In 1971 Worth described 2 cases of transitional cell carcinoma arising in patients who had had cyclophosphamide haemorrhagic cystitis, and Marsh (Marsh *et al.*, 1971) has reported a case of haemorrhagic cystitis following 60 g of cyclophosphamide in which the transitional epithelium showed necrosis and calcification. In this case contracture of the bladder and vesico-ureteric reflux had occurred. In addition the urethra and vulva were affected. Colocystoplasty was carried out. Liedberg (Liedberg, Rausing and Lange-land, 1970) reported 11 cases of cyclophosphamide haemorrhagic cystitis, 8 of whom died. Death was attributed directly to the condition in 2 cases and in 2 others haematuria was present at the time of death. Miller (Miller, Williams and Leissring, 1971) has reported a case in which the upper urinary tract was affected. Focal submucosal haemorrhages were found at or near the tip of nearly every papilla and scattered throughout the pelvis. Clots were present in the left ureter.

Spechter (Spechter *et al.*, 1965) reported a series of 444 women with tumours of the genital tract. 43 developed cystitis after the administration of cyclophosphamide for more than 1 month. In 10 of these the cystitis contributed to death. Another 10 women, with abnormalities of the renal

pelvis or parenchyma, developed acute or irreversible renal failure following cyclophosphamide treatment.

Rubin and Rubin (1966), Wiseman and Hambly (1971) and Marsh *et al.* (1971) have reviewed the literature on cyclophosphamide cystitis, and its incidence seems to vary between 10% and 40%. It does not appear to be dose dependent.

The *characteristic findings* are of sterile urine, an I.V.P. which may show an irregularly contracted bladder and an oedematous, hyperaemic mucosa, often with haemorrhagic areas, on cystoscopy.

Treatment of cyclophosphamide cystitis logically consists of preventing the metabolites of the drug acting on the bladder mucosa and withdrawal of the drug alone is usually sufficient. As a routine it is important to try to prevent the occurrence of cystitis by administering cyclophosphamide early in the day in association with a high fluid intake (B.M.J. leader, 1971). The development of symptoms of cystitis in any patient taking the drug should lead to its immediate withdrawal. The third patient whose case history we have reported is unusual in that resolution of the condition did not follow withdrawal of the drug, perhaps because such a large amount (170 g) had been given, although this was over a 9-year period.

When the problem is of haemorrhage, more active measures may be necessary and ureteric intubation (Reynolds *et al.*, 1969), cutaneous ureterostomy and open cystotomy with tamponade have all been used. Ligation of the hypogastric vessels is useless (Nagel and Baumgartel, 1968), but Lapides (1970) has stated that fulguration of the bleeding vessels should be feasible, but was impossible in the case reported here. In 1967 Anderson, Cobb and Glenn reported a case requiring cystectomy and ileal loop urinary diversion and this was our choice of treatment. Shortly afterwards Helmstein (1972) described a new technique in the treatment of bladder tumours involving hydrostatic pressure: this produced a marked reduction in blood flow in the bladder wall and caused sloughing of the tumour. This method might have a place in the treatment of cyclophosphamide haemorrhagic cystitis which has not responded to withdrawal of the drug.

Summary

Cyclophosphamide may cause fibrosis of the bladder in a significant number of patients. Most will be asymptomatic but the fibrosis can lead to reflux. Cystitis, frequently haemorrhagic, occurs in 10-40% of patients and usually responds to withdrawal of the drug. Active measures to stop the bleeding may be required.

Bleeding from the upper urinary tract is rare.

The association of bladder tumours with cyclophosphamide cystitis has been reported in only 2 cases.

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An Evaluation of Otis Urethrotomy in Female Patients with Recurrent Urinary Tract Infections

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Urinary tract infections in women are a common and recurring problem. The long-term results of treatment with antibiotics, urinary antiseptics and urethral dilatation are disappointing; and any symptomatic relief obtained is, for the majority, only transient. Yet these methods are the mainstay of treatment for these women.

Internal urethrotomy has been advocated as an alternative form of treatment, and reports in the American literature of its use both in adults (Kerr, Leadbetter and Donahue, 1966; McLean and Emmett, 1969; Keitzer and Allen, 1970; Immergut and Gilbert, 1973*a*) and children (Kerr *et al.*, 1966; Vermillion, Halverstadt and Leadbetter, 1971; Immergut and Gilbert, 1973*b*) have been encouraging: but it has not gained wide acceptance in this country. Since 1968 however internal urethrotomy, with the Otis urethrotome, has been part of the urological armamentarium in Norwich. This paper presents our experience with its use in females with recurrent urinary tract infection, with particular emphasis on the long term results of treatment.

Patients and Procedure

200 patients, whose ages ranged from 4½ to 85 years, and who underwent internal urethrotomy at the Norfolk and Norwich Hospital between September 1968 and April 1971 were studied.

Patients in Series

The ages of the patients are shown in the Figure; 95% were married.

All the patients had symptoms of recurrent urinary tract infection, although in only 44% was there evidence of infection in a mid-stream urine examined at the initial assessment. On the basis of their main presenting symptoms the patients were divided into 5 main groups (Table I) and the results of treatment were assessed separately for each group.

Three patients were excluded from the series when they were found to have interstitial cystitis; 4 patients died of causes unrelated to their urinary tract infections, and 26 did not reply to the questionnaire. 167 patients completed a minimum 2 year follow-up. All the patients initially underwent routine investigations including haemoglobin, blood urea and creatinine estimations, a routine urinalysis and an intravenous pyelogram. A micturating cystogram was done in some cases. The urethra was calibrated with *bougie à boule* with the patient under a general anaesthetic, prior to a routine cystoscopic examination of the bladder. At the conclusion of the cystoscopy the bladder was left partially filled and the Otis urethrotome introduced into the bladder. Full length cuts of the urethra to a depth of 2 mm were made at the 12, 3, and 9 o'clock positions with the urethra stretched to 30F, 35F and 40F respectively, and in some cases to 45F. In children the final cut did not exceed 25F. An 18F Foley catheter was used following the urethrotomy because of the urethral bleeding, and removed the next day. The patient was discharged home when voiding, taking antibiotics usually for 6 weeks, but at times for 3 months.

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Routine follow-up was at out-patients 6 to 12 weeks after the urethrotomy, but further follow-up for this series was by postal questionnaire. Patients were asked whether they considered their symptoms following the urethrotomy to be cured, improved, no better or worse.

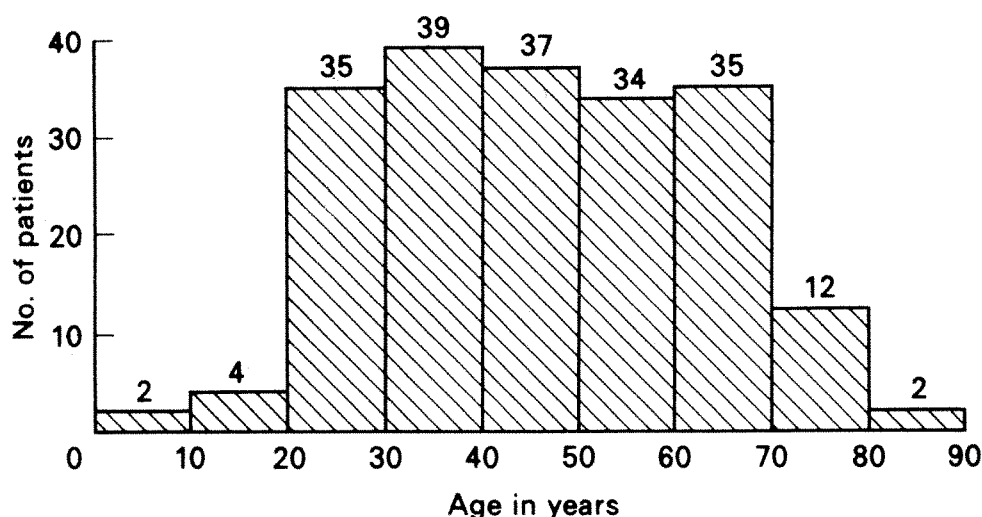


Figure. Ages of patients at time of urethrotomy.

Table I

Presenting Symptoms of 200 Patients Studied

	No. of Cases
I Recurrent cystitis—Children	2
Adults	123
II Frequency/Urgency	31
III Upper tract symptoms	13
IV Incomplete emptying of bladder	10
V Retention—Acute	5
Chronic	12
Miscellaneous:	
Stress incontinence	1
Enuresis in adult	1
Urethral pain	1
Frequency following caecocystoplasty	1
	200

Results

Table II shows the results of treatment in those patients who presented with symptoms mainly of recurrent cystitis. The 2 children in this group were improved at a 3 and 4 year follow-up respectively; 1 child was cured of her severe ureteric reflux by the urethrotomy.

The results in patients who presented with frequency and urgency are shown in Table III. The initial improvement of symptoms at 6 months was not maintained at a 2 year follow-up; of the 13 patients who were no better at this time 11 were post-menopausal.

Table IV shows the results in patients whose main symptoms were confined to the upper urinary tract; and Table V the results of those who felt evacuation of the bladder was incomplete. In both cases the results at a 2 year follow-up were good.

Five patients presented with acute retention of urine, and all but 1 benefited from the urethrotomy. Two patients who were followed up for 2 years and subsequently for 3 years had not relapsed. However only 6 of the 12 patients who presented with chronic retention were improved, although the improvement was maintained at 2 years for 4 patients; and 4 years for 2 patients.

Table II

Results of Treatment of Patients with Recurrent Cystitis

Length of Follow-up	Total No. of Cases	Results of Treatment		
		Cured	Improved	No Better
6 months	113	35 (31%)	67 (59%)	11 (10%)
1 year	108	34 (31%)	58 (53%)	16 (16%)
2 years	105	31 (29%)	49 (47%)	25 (24%)
3 years	65	15 (23%)	34 (52%)	16 (25%)
3½ years	32	6 (19%)	18 (56%)	8 (25%)
4 years	9	1 (12%)	6 (66%)	2 (22%)

Table III

Results of Treatment of Patients with Frequency/Urgency

Length of Follow-up	Total No. of Cases	Results of Treatment		
		Cured	Improved	No Better
6 months	28	5 (18%)	16 (57%)	7 (25%)
1 year	26	4 (16%)	10 (38%)	12 (46%)
2 years	26	4 (16%)	9 (34%)	13 (50%)
3 years	14	3 (21%)	3 (21%)	8 (58%)

Table IV

Results of Treatment of Patients with Upper Tract Symptoms

Length of Follow-up	Total No. of Cases	Results of Treatment		
		Cured	Improved	No Better
6 months	12	5 (42%)	5 (42%)	2 (16%)
1 year	12	5 (42%)	5 (42%)	2 (16%)
2 years	11	4 (36%)	5 (46%)	2 (18%)

In the final miscellaneous group (Table I), the patient with stress incontinence was improved 3 months after the urethrotomy but was then lost to follow-up. Urethrotomy was not however usually performed in patients with symptoms of bladder neck incompetence. The other 3 patients in this final group did not benefit from the urethrotomy.

The overall results of all the cases in this series are shown in Table VI. No patient was made permanently worse by the procedure.

Urethral Calibre. This was less than 25F in 62% of cases. Urethrotomy was not routinely performed in this series if the urethral calibre was greater than 30F. There was no correlation between the results of treatment and urethral calibre.

Table V

Results of Treatment of Patients with Incomplete Evacuation

Length of Follow-up	Total No. of Cases	Results of Treatment		
		Cured	Improved	No Better
6 months	10	4 (40%)	5 (50%)	1 (10%)
1 year	10	4 (40%)	5 (50%)	1 (10%)
2 years	10	4 (40%)	5 (50%)	1 (10%)
3 years	6	3 (50%)	3 (50%)	0 (0%)

Table VI

Overall Results of Treatment of Patients Studied

Length of Follow-up	Total No. of Cases	Results of Treatment		
		Cured	Improved	No Better
6 months	180	54 (30%)	97 (54%)	29 (16%)
1 year	173	52 (30%)	82 (48%)	39 (22%)
2 years	167	46 (27%)	73 (44%)	48 (29%)
3 years	94	25 (26%)	43 (46%)	26 (28%)
3½ years	47	13 (28%)	19 (40%)	15 (32%)
4 years	17	3 (18%)	7 (41%)	7 (41%)

Table VII

Complications Following Urethrotomy

	No. of Cases
Excessive urethral bleeding	1
Temporary stress incontinence	3

Complications. The urethrotomy was repeated in 15 cases, and 2 patients had a third urethrotomy; so that a total of 219 urethrotomies were performed and complications followed only 4 of these (Table VII). The excessive urethral bleeding in 1 case did not require a transfusion. The post-operative stress incontinence was severe in 1 case and took 4 months to settle, but in the other 2 cases was mild and settled in a few days. In 1 of these cases the urethrotomy was subsequently repeated with no further complications. Bacteraemia or septicaemia were not a problem following the urethrotomies.

Discussion

Urethral stenosis would appear to be an important aetiological factor in females with recurrent urinary tract infections, and has been demonstrated in both adults (Bonnin, 1969; McLean and

Emmett, 1969) and children (Lyon and Smith, 1963) mainly to be in the distal third of the urethra. It is probable that the degree of stenosis is relative and depends to some extent upon detrusor function and it is therefore difficult to define the normal urethral calibre (Hole, 1972). Kerr *et al.* (1966) have gone so far as to state that an adult female urethra of less than 40F constitutes a relative urethral stenosis. There has however been reluctance to stretch the urethra to this size because of the fear of permanent incontinence. This fear was not borne out in this series where the complication rate was less than 2% and others report similar low complication rates (Kerr *et al.*, 1966; McLean and Emmett 1969) even when the Otis knife was used to 46F routinely (Keitzer and Allen, 1970; Immergut and Gilbert, 1973a).

In the assessment of the results of treatment, it was felt justified to rely on the patient's symptoms rather than the bacteriology of the urine, as at an initial screening less than half the patients had demonstrable evidence of infection despite marked symptoms. Overall both the short- and long-term results of treatment were good: 71% of patients had benefited at 2 years and 68% at 3½ years with 28% of patients cured of their symptoms. Similar results were found in the largest subgroup, those with symptoms of recurrent cystitis, with 76% benefiting at 2 years and similarly at 3½, with 25% cured. However in those patients who presented with symptoms of frequency and urgency the long-term results were disappointing, although of those patients who were not improved the majority were post-menopausal and an associated oestrogen deficiency may in part have accounted for their failure. Even so 16% of the patients in this group were cured at 2 years. On the contrary in patients with chronic retention the initial failure rate was high but there was no relapse in those who benefited.

A measure of the long-term effectiveness of Otis urethrotomy is that it was necessary to repeat it in less than 9% of cases; and then with no complications. Unfortunately it was not possible to predict on urethral calibre alone those who would benefit from the urethrotomy. The voiding cystogram may be a better guide to the presence of a relative outflow tract obstruction (Turner Warwick and Whiteside, 1967), but on the whole internal urethrotomy remains empirical, dictated by the patient's symptoms.

Conclusion

As a treatment for females with recurrent urinary tract infection, internal urethrotomy is a simple and safe procedure which gives prolonged long-term benefits superior to other commonly used forms of treatment, and is worthy of wider acceptance.

Summary

200 female patients who underwent internal urethrotomy with an Otis urethrotome have been studied. 68% of patients had benefited at a 3½ year follow-up and it was necessary to repeat the procedure in less than 9% of cases. Complications occurred in less than 2% of cases and were mild.

We would like to thank Miss J. Birch and Mrs S. Green for their secretarial assistance.

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Discussion

MR ROGER HOLE (*Teesside*)

I am sorry to see that no controls were used, but in this you are in good company for, to my knowledge, there is no report in the literature of controls being used when a surgical treatment for recurrent frequency and dysuria is reported.

I have recently reviewed a small retrospective series of women all of whom had at least a 9-month history of frequency and dysuria. They were all cystoscoped by one surgeon (myself) using a 21F or a 24F cystoscope: no treatment of any sort was given though they were all carefully reassured of the absence of serious disease and where appropriate, those with sexual difficulties were given suitable advice. At least 2 years after cystoscopy their symptoms were reassessed by postal questionnaire. This showed that 30% had had no symptoms at all in the preceding 2 or 3 years, a further 51% had had some symptoms but they thought that these were less troublesome than before the cystoscopy. With a total of 81% either cured or improved these results strongly suggest that "Nothing works better than internal urethrotomy".

The Association of Bladder Dysfunction with Degenerative Lumbar Spondylosis

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Lumbar backache and root pains caused by prolapsed intervertebral disc have long been recognised. More recently (Ehni, 1969; Paine and Haung, 1972) neurosurgeons have described a similar neurological presentation where the spinal disorder is a degenerative arthritis of the posterior interlaminar joints with secondary changes leading to a narrowing of the spinal canal. These changes are most commonly found in the lumbar spine and the condition has been given the name "degenerative lumbar spondylosis".

Whilst urinary symptoms in association with prolapsed intervertebral lumbar disc have been fully described, it is not generally recognised that degenerative lumbar spondylosis is also a cause of neurogenic bladder dysfunction. This paper describes 17 patients who have undergone laminectomy for degenerative lumbar spondylosis, all of whom had significant urinary flow abnormalities.

Clinical Material

Details of the 17 patients are set out in the accompanying table. It can be seen that degenerative lumbar spondylosis is not exclusively a disease of the aged. Nine of the 17 patients were aged 60 or under. Eight of the 17 were referred directly to a Urological Clinic by the general practitioner rather than to a Neurological or Orthopaedic Department for spinal symptoms.

Urological Presentation

Urological symptoms were: recurrent infection which was nearly always associated with an atonic bladder; incontinence, either overflow incontinence or total emptying; and episodes of acute retention. The onset of urological symptoms did not always coincide with the onset of spinal symptomatology. In 6 patients spinal symptoms preceded the onset of urinary troubles. In 7 patients urological and spinal symptoms appeared at the same time. Two patients did not complain of spinal symptoms although examination revealed neurological abnormalities.

An additional feature of the urinary symptoms was their intermittency. For example, patient I. M. (No 13 in the Table), had continuous daily frequency but at times of physical stress, notably when lifting heavy weights, had apparent sudden, involuntary total emptying of the bladder. Patient M. I. (No 10) though suffering from continual urge, had sudden bouts of involuntary total incontinence brought on by walking short distances and coinciding with leg weakness. Intermittency of symptoms (in some of these patients) may account for the apparently normal cystometry in 4 patients (Nos. 7, 8, 9 and 15).

Spinal and Neurological Presentation

12 patients gave a history of low back pain for many years, and in several for more than 20 years, symptoms which had not led them to seek medical advice. 11 patients had motor or sensory symptoms of root distribution related to exercise such as walking and relieved by standing, this

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being consistent with claudication of the conus or cauda equina (Blau and Logue, 1961). Only 6 patients had significant neurological deficit in the lower limbs or perineal sensory loss.

Urological Investigations

Most patients underwent full urological investigations which included urinalysis, urography, cystoscopy and cystometrogram.

Intravenous urography showed a large residual urine when present, and demonstrated that the upper urinary tracts were normal in all patients. The appearances of the lumbar spine on the control films were noted, and in all cases full radiography of the lumbar spine was done later as part of the neurological investigations.

Cystoscopy was done in all patients after instillation of lignocaine gel into the urethra. Residual urine was measured and the absence of anatomical outflow obstruction confirmed in all cases. At the same time the presence or absence of sensation produced by touching the trigone with the cystoscope was noted. In 5 patients, sensation was grossly reduced.

Cystometry was performed on most patients using the technique of filling the bladder at a constant rate of 50 ml/minute via a bottle on a drip stand through a 12 F.G. Foley catheter attached to a manometer. Rectal pressures and urethral pressure profiles were not measured.

With this simple technique 2 major abnormalities were demonstrated.

1. In 7 patients a large atonic bladder, filling to more than 1 litre with no desire to void and without rise in pressure.
2. In 2 patients, cystometry showed a rapid increase in pressure on filling with uninhibited high pressure waves. In 4 patients cystometry was normal.

Neurological Investigations

All patients had plain radiographs of the whole spine. The significant findings in the lumbar region included severe degenerative changes in the interlaminar joints. Roberts (1973) has drawn attention to measurements of the sagittal diameter and the cross-sectional area of the lumbar canal, which were significantly reduced in these patients and therefore an important factor in the stenosis of the lumbar canal. Positive contrast myelography using myodil showed abnormalities varying in severity from complete obstruction to postero-lateral and anterior indentations of the myodil column at single or multiple lumbar intervertebral levels (see Fig. 1, A and B).

Surgical Treatment

In the presence of neurogenic bladder dysfunction, the necessity for and the extent of decompressive lumbar laminectomy was indicated by the severity and extent of the myelographic abnormalities. The main operative findings were constriction of the theca by greatly enlarged posterior interlaminar joints and by thickened ligamenta flava which lay not only posteriorly but also antero-laterally to the dural sac. A wide decompressive laminectomy of up to 5 vertebrae was performed with removal of the medial facets of the enlarged joints when necessary.

Results

Follow-up has been from 9 months to 3 years. One patient died 18 months after laminectomy. The cause of death is unknown. From the urological aspect there has been considerable symptomatic improvement in 13 of the 17 patients (see table).

Cystometry has been repeated when possible and a return to normal has been noted in 6 patients who previously had had large atonic bladders with large residual urine volumes. Of the

2 patients with an upper motor neurone type of bladder disturbance encountered, 1 has returned to a normal cystometry pattern after surgery.

Neurological improvement has been less marked, but 9 patients have shown good symptomatic improvement.

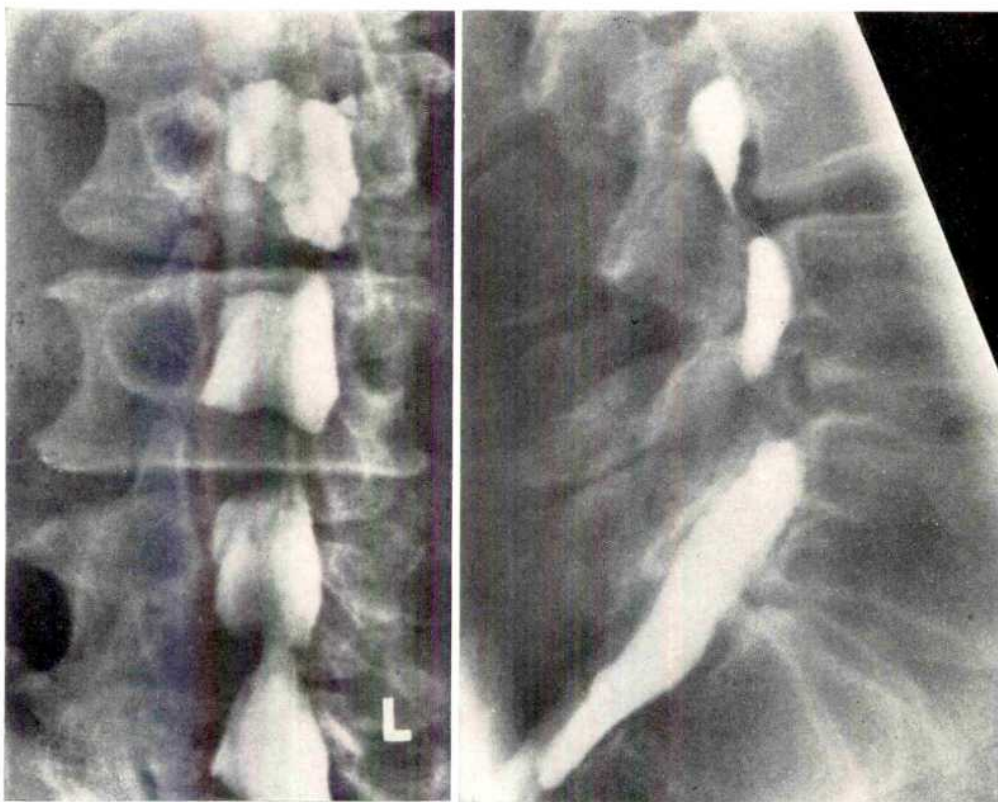


Fig. 1. Positive contrast myelogram, patient erect, showing attenuation and fragmentation of contrast column due to enlarged posterior interlaminar joints. **A**, Antero-posterior. **B**, Lateral.

Discussion

In recent years awareness of degenerative lumbar spondylosis as distinct from prolapsed lumbar disc has grown. The important neurological features of degenerative lumbar spondylosis, with due emphasis on chronic back pain, and its distinguishing features from prolapsed lumbar disc were stressed by Teng and Papatheodorou (1963).

The significant pathological features which contribute to the narrowing of the lumbar canal include striking enlargement of the interlaminar joints, thickening of the ligamenta flava and bony bars between the posterior margins of the vertebral bodies. These features lead to a change in the shape of the lumbar canal which becomes trefoil. An additional factor in the compression is the pre-existing sagittal diameter of the canal.

In previous accounts of this condition little attention has been paid to the urinary symptoms. Paine and Haung (1972) described 227 patients with lumbar disc syndrome severe enough to warrant surgery, of whom 65 had degenerative lumbar spondylosis, but there is no mention of urinary disturbance. In the present smaller series urinary symptoms appear to predominate in

Table

Name and Age	Presentation To	Neurological Symptoms	Urological Symptoms	Neurological Examination	Cystometry Findings	Follow-up		
						Urological	Neurological	Time
No. 1 J. K. Male	Urologist	Claudication 10 yrs. low back pain radiating to buttocks	Poor stream and retention 6/12	Mild leg weakness. Saddle sensory loss	Atonic bladder	Good flow. Normal cystometry	No change	3 yrs
No. 2 C. H. Male	Urologist	Nil	8/12 incontinence	Weak ankle. Dorsiflexors. Absent ankle jerks. Saddle sensory loss	...	Died?	Cause	...
No. 3 A. W. Male	Neurologist	5 yrs low back pain, leg pain and weakness	2 yrs urgency and incontinence	Flaccid paraparesis, sensory level L 1/2	...	Some improvement, but still stress incontinence	No change	3 yrs
No. 4 W. T. Male	Neurologist	5/12 low back pain, R. leg pain and weakness	1 yr poor stream, nocturia and intermittent retention	Very weak areflexic R. leg	...	No further retention	No change	3 yrs
No. 5 N. A. Male	Urologist	3 yrs pain in legs and claudication	1 yr incontinence and impotence	Normal	Atonic bladder	No longer impotent. Continent. Cystometry normal	Asymptomatic. No pain and no claudication	9/12
No. 6 D. S. Male	Urologist	1 yr weakness L. leg	6/12 dribbling incontinence. Post-prostatectomy overflow	Spastic weak L. leg. Extensor plantar responses	No sensation. Atonic bladder	Fully continent and no dribbling	L. leg still weak but better since surgery. Continues to improve	9/12
No. 7 C. S. Male	Neurologist	2 yrs backache and pain in legs	1 yr dribbling and incontinence	Minimal wasting of glutei and thighs	Apparently normal	No symptoms. Continent.	Asymptomatic. No pain and no claudication	9/12
No. 8 M. G. Female	Neurologist	3 yrs backache and R. leg pain	3/12 incontinence and frequency	Weak R. leg (slight)	Normal	No change	No change	1 yr
No. 9 D. R. Female	Neurologist	1 yr backache and leg weakness	1 yr symptoms of U.T.I. and bouts of incontinence	Weak hip flexors, brisk knee jerks and absent ankle jerks. Equivocal plantars	Normal	Asymptomatic	Improved	2 yrs
No. 10 M. I. Female	Urologist	Many years backache and L. leg pain	For years incontinent infloods. (Uninhibited)	Mild weakness L. Hip. Absent ankle jerks	Grossly abnormal. Upper motor neurone type	Continent. Cystometry normal	Improved	18/12
No. 11 J. U. Female	Neurologist	9/12. R. groin pain	Many years symptoms of frequency	Normal	Abnormal. Atonic. Sensation absent	Symptom free. Normal cystometry	Symptom free	9/12
No. 12 M. D. Female	Neurologist	10 yrs low back pain	For many years urgency with symptoms of U.T.I.	Mild reduction of sensation outer side of calves	...	Symptom free	Symptom free	2 yrs
No. 13 I. M. Female	Urologist	15-20 years low back pain, ache buttocks	Incontinence and flooding for many years (uninhibited)	Normal	Grossly abnormal. Atonic with no sensation	Symptom free. Cystometry normal	Occasional low backache only	2 yrs
No. 14 E. P. Female	Urologist	2 yrs low back pain	2 yrs symptoms U.T.I.	Normal	Grossly abnormal. Atonic with no sensation	Improved. Normal cystometry	Occasional backache only	3 yrs
No. 15 J. V. Female	Neurologist	Many years backache and bilateral sciatica	3 yrs U.T.I.	Normal	Normal	Improved—occasional frequency	Improved—occasional backache	18/12
No. 16 G. A. Female	Urologist	...	2 yrs incontinence	Weak glutei, saddle loss, Absent ankle jerks	Abnormal, upper motor neurone type	No change	No change	1 yr
No. 17 R. N. Female	Neurologist	For years backache. For years pain L. leg	Many years U.T.I.	Normal	Abnormal. Atonic. Absent sensation	Symptom free. Cystometry normal	Occasional backache only	8/12

that nearly half of the patients were referred initially to a urological clinic, the spinal symptoms being discovered secondarily. It is emphasised also that the spinal symptoms and signs of degenerative lumbar spondylosis can be limited to backache alone, with little abnormality on neurological examination. This may be due to the intermittency of the symptomatology, for it is known that cauda equina claudication of which degenerative lumbar spondylosis is an important cause, is typically brought on by exertion. Intermittency of urinary symptoms is also a feature of this series and may explain the normal cystometrogram on several patients. The simple method of cystometry used may also have precluded detection of subtle changes in bladder function. Since the present series, more patients have been seen and a transducer method of cystometry with subtraction of the intra-abdominal (rectal) pressure has been employed. However, with this more sophisticated method, no further information has yet been obtained, and it is likely that simple methods will suffice to detect most cases of neurogenic bladder dysfunction.

Upper motor neurone bladder dysfunction has recently been described by Jones and Moore (1973) in association with lumbar disc protrusion. In their opinion an uninhibited bladder is the first "irritable" stage of a progressive disorder of bladder function, which if left untreated would lead to an atonic bladder, as compression increased. Two patients with this type of bladder dysfunction have been treated in this series. One had the disturbance for many years, and it therefore seems more likely that the level of the compression was more important than the degree of compression.

Where a case of neurogenic bladder has been encountered it has been the practice to call for consultation with the neurosurgical department early in the management of the patient. This practice has resulted in some "false alarms" but in the main it has been found most useful. Plain X-rays of the lumbar spine have been studied together and a decision whether to proceed to myelography taken on the urological and neurological evidence combined with the appearances on the plain film.

The myelographic appearances of degenerative lumbar spondylosis are diagnostic and it is on these appearances that the decision to perform laminectomy and its extent is made.

Summary

17 patients with urinary symptoms caused by degenerative lumbar spondylosis are described.

Treatment has been lumbar laminectomy in all patients. The need for close co-operation between urologists and neurosurgeons in the selection of cases for surgery is stressed.

Laminectomy has produced relief of urinary symptoms in 13 of 17 patients.

Degenerative lumbar spondylosis is an important cause of bladder dysfunction and should be considered in any patient in whom a local disorder has been excluded, even in the absence of significant neurological deficit.

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The Effect of Urethral Lengthening

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The mechanisms maintaining closure of the female urethra remain poorly understood. The bladder neck is the primary sphincter and closure is due to the activity of smooth muscle (Tanagho, Smith and Meyers, 1968) and elastic tissue (Lapides, 1958; Woodburne, 1960). Although it has been thought that the urethra must measure 2-3 cm in length for the primary vesical sphincter to maintain continence (Lapides, 1958), Ardran *et al.* (1967) showed, in an experimental study using dogs, that continence was maintained after excision of the whole urethra, unless reflex voiding was produced. Though the actual length of the urethra is not vital for continence, it is widely held that mechanical lengthening increases urethral closure pressure (Harrison and Paterson, 1970; Edwards, 1971). It is postulated that the fibres of the female urethra are arranged helically and hence tighten when the urethra is elongated (Mitchell, 1972; Yeates, 1972) (Fig. 1). This structural arrangement, however, has never been demonstrated

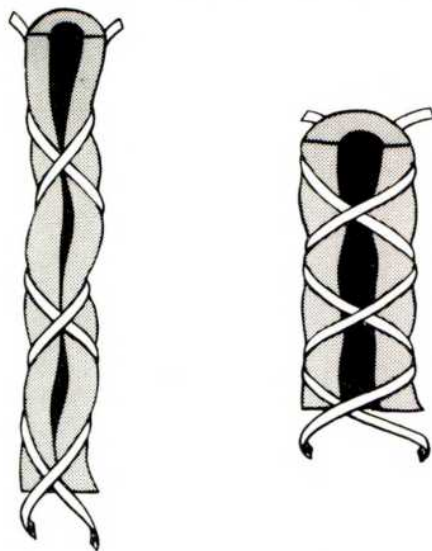


Fig. 1. Diagram showing the possible spiral arrangement of muscle fibres in the urethral wall. The lumen is narrowed when the urethra is lengthened.

microscopically. However, the functional orientation of the components of the urethral wall can be determined by demonstrating how the closed urethra responds to inflation. Material such as rubber, which has the same modulus of elasticity whatever the direction of the applied force, is said to be isotropic. If a closed rubber tube is inflated, it neither lengthens nor shortens. Up to now, blood vessels are the only biological tubes which have been studied in this way: the more muscular arteries tend to elongate slightly when held at *in vivo* lengths and inflated to physiological pressures. That is to say they are anisotropic, being stiffer circumferentially (Patel and Janicki, 1970). Therefore, if the closed urethra lengthens beyond its *in vivo* length when inflated

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within its usually physiological pressure range, it is anisotropic, the circumferential elements being stiffer than the longitudinal ones.

An experiment was designed to test this assumption: the response to filling urethral segments from female dogs was compared with isotropic latex rubber tubes under the same experimental conditions. In a second experiment, the response of the urethra and latex rubber tube to mechanical lengthening was determined by noting the change which occurred in intraluminal volume when the urethra was lengthened at various fixed filling pressures.

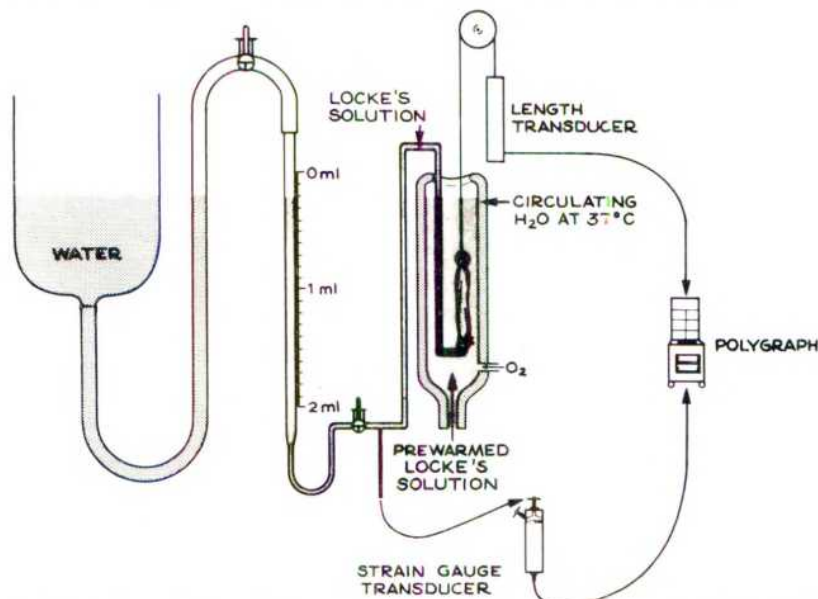


Fig. 2. Diagram of the apparatus used in *in vitro* experiments with segments of dogs' urethras or latex rubber tubes. In the experiments where the length of the segments was mechanically changed, the top of the specimen was tied on to a glass rod to which the length transducer was also attached.

Response to Inflation

Materials and Methods

The urethra was removed under pentobarbital anaesthesia from 10 female mongrel dogs weighing 25-49 lbs. The symphysis pubis was excised and any fat present was dissected away to expose the anterior surface of the urethra. Care was taken to avoid traction on the urethra or bladder. A 3 cm segment between the bladder neck and the pelvic floor was marked with fine silk sutures. The urethra was then divided at least 0.5 cm on either side of the marking sutures and separated from the vagina and uterus posteriorly, which required very little dissection. The segment of urethra was then transferred to an organ bath (Fig. 2).

The bath had a volume of 50 ml and contained Locke's No. 2 solution¹ which was changed regularly with fresh pre-warmed solution and perfused continuously with oxygen. One end of the urethra was tied securely at the level of one marker over the glass tube at the bottom of the bath and, after exclusion of any air in the system, the other end was closed at the level of the other marker. The closed urethral segment *in vitro* thus represented the 3 cm segment in the intact animal. The upper end was attached by a silk thread to the central core of a differential transformer over a low friction pulley. The differential transformer (length transducer) provided a linear response and could be calibrated to read to 1 or 2 cm full scale. The weight of the central core was counterbalanced so that only 0.5 g tension was exerted on the urethral segment. Locke's No. 2 solution was instilled into the urethra by raising the reservoir. The air-lock enabled the volume change to be read off the graduated scale. Pressure in the system was measured at a point between the graduated scale and the specimen by a line leading to a pressure

¹ Locke's No. 2 solution consists of: NaCl 9.0, KCl 0.42, CaCO₃ 0.24, NaHCO₃ 0.3, dextrose 1 g/l.

transducer (Sanborn, Waltham, Mass., USA, Model 267 BC). Intraluminal pressure and length were displayed on 2 channels of a 4-channel recorder (Statham Model No. 154-100 BP). Volume change was read from the graduated scale and noted on the chart.

Zero volume and pressure were obtained by first opening the tap in the air-lock so that the graduated column was open to air. The column was then filled to just above zero level (the top level of the water bath) with Locke's No. 2 solution by inserting a syringe into the tap between the graduated column and the specimen. The specimen was also distended with a small quantity of fluid which was then allowed to run out through the tap after removal of the syringe. When all the fluid had leaked out of the urethra, the tap was closed to air so that the graduated column and the urethra were now connected. Finally, the tap in the air-lock was closed to air, thus connecting the reservoir and the graduated column.

When the urethra had been in the organ bath for 30 minutes the resting length was measured. Three inflation cycles to 25 cm H₂O were then performed. Any ensuing lengthening was recorded, and the hysteresis response was stabilised (Remington, 1957). In 4 specimens detailed data were obtained on the length and intraluminal volume change in response to incremental pressure increases. Three further inflation cycles were performed, the pressure being raised from 0 to 25 cm H₂O in 5 cm H₂O increments every minute. Intraluminal volume was read at the end of each 1-minute interval. In 1 experiment both inflation and deflation cycles were performed to document the hysteresis response but, with the other 3, only inflation cycles were done.

At the end of the experiment, the urethra was taken from the organ bath and excess tissue at the ends was cut away, so that only the marked segment remained. It was opened and weighed in air, then in water, to obtain the initial volume. It was noted that the specimen assumed a uniform circular shape on inflation, and since the total volume (initial volume of specimen + intraluminal volume) and the total length (initial length + incremental length) were known, the external circumference at any increment of pressure could be calculated.

The urethral response to inflation was compared with the response of three latex rubber tubes of similar size. The length of these tubes was approximately 3 cm, their external diameter 0.8 cm, and their wall thickness 0.035 cm. The experimental protocol was exactly the same as that for the urethral experiments except that inflation was taken to a pressure of 50 cm H₂O.

Results

First, the resting length of the urethra was measured after the specimens had been in the organ bath for 30 minutes at zero filling pressure. Six urethrae shortened, 3 remained unchanged and 1 lengthened. After 30 minutes in the organ bath the mean length was 2.86 cm (S.D. 0.224 cm) compared with an *in vivo* length of 3.0 cm—which indicates there is minimal longitudinal traction on the urethra *in vivo*. There was no change in length of the latex rubber tube after it had been in the organ bath for 30 minutes.

In all 10 urethral specimens obvious lengthening occurred on inflation (Fig. 3). In the 4 specimens where data were obtained for incremental pressure increase, percentage change in external circumference was calculated from volume and length measurements. When percentage change in length and circumference were both plotted against pressure, not only did the urethra lengthen but a greater percentage change occurred in length than in circumference (Fig. 4): in neither case is the response linear, a fact consistent with the nature of biological material. The gradient of the curves gradually decreases with augmented pressure, but even at 25 cm H₂O pressure, lengthening is still occurring. This marked change in length when compared with change in circumference was found in all specimens above 5 cm H₂O pressure (Fig. 5). Thus the urethra is anisotropic.

When the latex tube was inflated, no lengthening occurred up to a pressure of 50 cm H₂O (Fig. 6), which confirms that latex rubber is isotropic material. At very high pressures lengthening appeared to occur but only because the tube had become spherical.

Effect of Mechanical Lengthening

Materials and Methods

The method of removal of the urethral segments and the arrangement of the apparatus was identical to that of the experiments on the response to inflation—with one exception. The upper

end of the specimen, instead of being free to lengthen, was attached to one end of an inverted U-shaped rigid glass rod, the other end of which could then be attached to the outside of the organ bath. The rod could be adjusted to any length and held there, and the length transducer

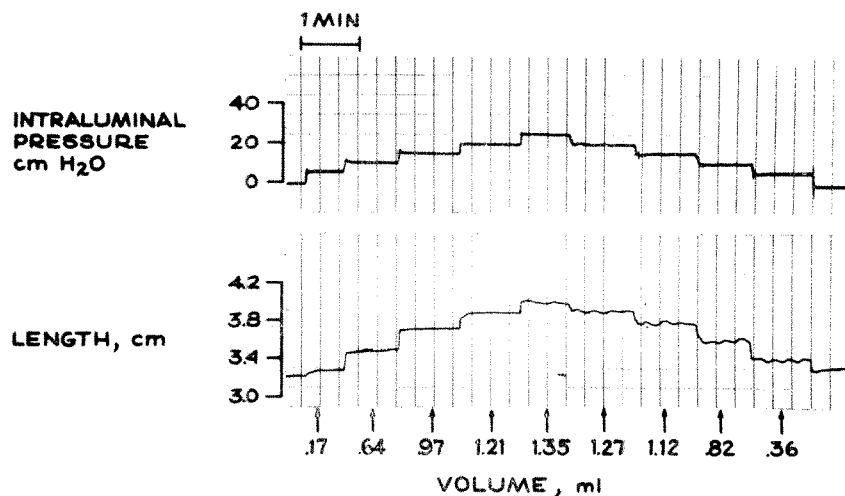


Fig. 3. Dog urethra, *in vitro*. Change in length and intraluminal volume following incremental increase and decrease of intraluminal pressure. Note: (1) the hysteresis effect—length and volume are greater during unloading; (2) spontaneous changes in length as pressure decreases.

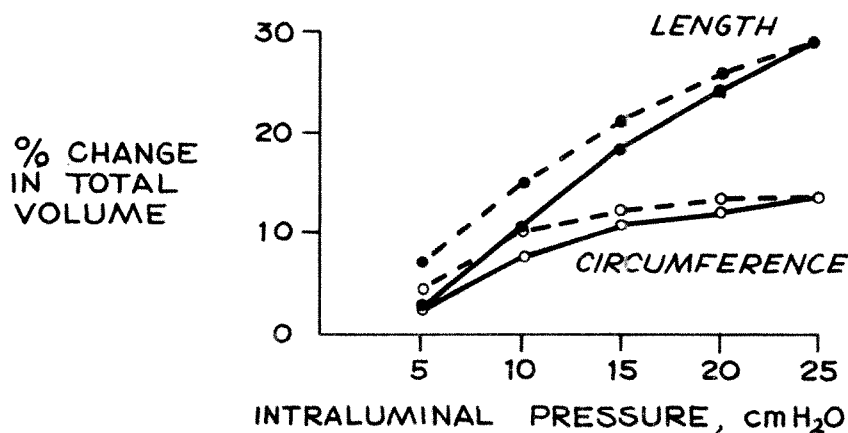


Fig. 4. Dog urethra, *in vitro*. Percentage change in length and circumference plotted against intraluminal pressure. Continuous lines are used as pressure increases (loading) and broken lines as pressure decreases (unloading). The hysteresis phenomenon is apparent.

was connected to the rod so that mechanical changes in length could be recorded. Three inflation cycles were performed to minimise the hysteresis response. The specimen was subjected to a certain filling pressure and the intraluminal volume read at one minute. Then the specimen was lengthened by 0.4 cm, held there for 1 minute and the volume was again recorded. Finally, the specimen was shortened back to its initial length and, after a further minute, the final volume was recorded. Various filling pressures were used for both urethral specimens and latex rubber tubes.

Results

When the urethra was filled at intraluminal pressures from 2.5 to 20 cm H₂O, mechanical increase in length was associated with an *increase* in intraluminal volume (Fig. 7). With the latex rubber

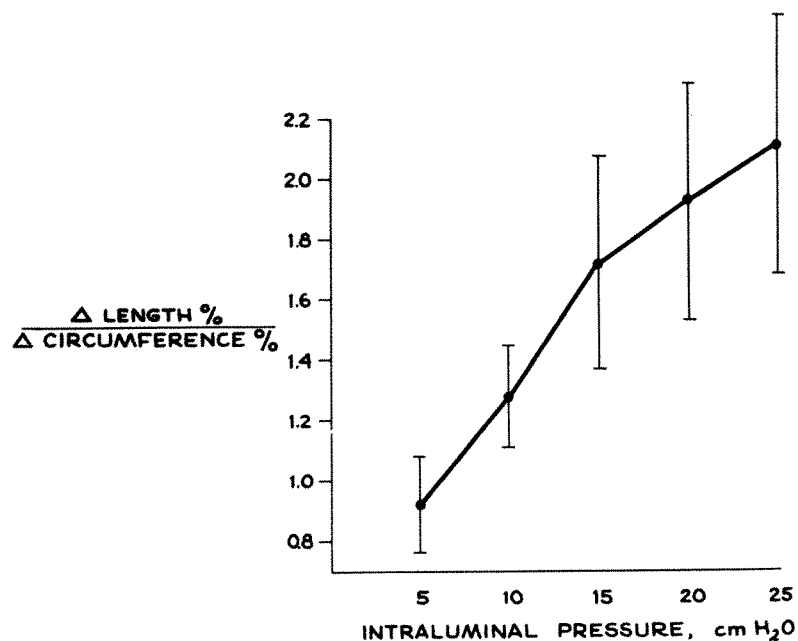


Fig 5. Dog urethra, *in vitro*. Ratio of percentage change in length and percentage change in circumference plotted against intraluminal pressure (means and standard deviations for 4 specimens).

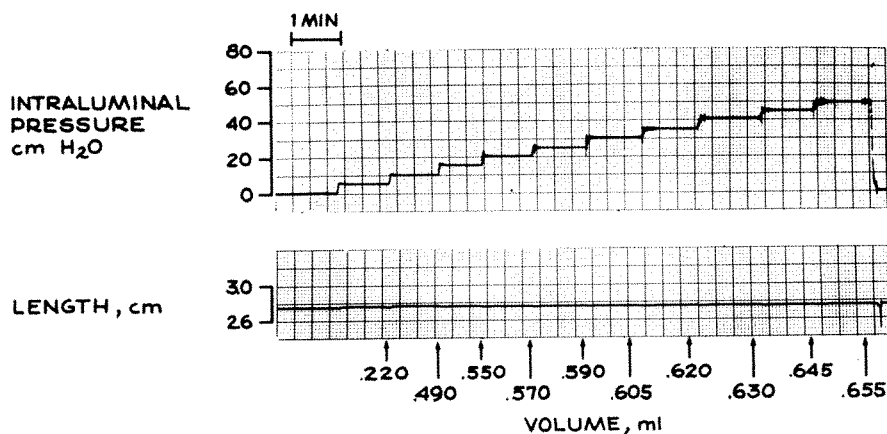


Fig. 6. Latex rubber tube. Change in intraluminal volume with incremental increase in intraluminal pressure in a 3 cm segment. Note that there is no change in length.

tube at a filling pressure of 30 cm H₂O, the reverse occurred—intraluminal volume *decreased* when the tube was lengthened (Fig. 8). The responses of a urethra and a latex rubber tube are illustrated in Figure 9. (The failure of the volume to return to the initial levels in both specimens on restoration of the initial length is due to hysteresis.) It can be seen that when the urethra is

lengthened intraluminal pressure tends to fall (Fig. 7) and that when the latex rubber tube is lengthened there is a tendency for pressure to rise (Fig. 8). These changes occur in spite of the presence of a large fluid filled reservoir. However, the air-lock could cause some damping of pressure from the reservoir to the specimen. The pressure line to the transducer comes from between the air-lock and the specimen and, in fact, probably measures the reactive pressure of the wall of

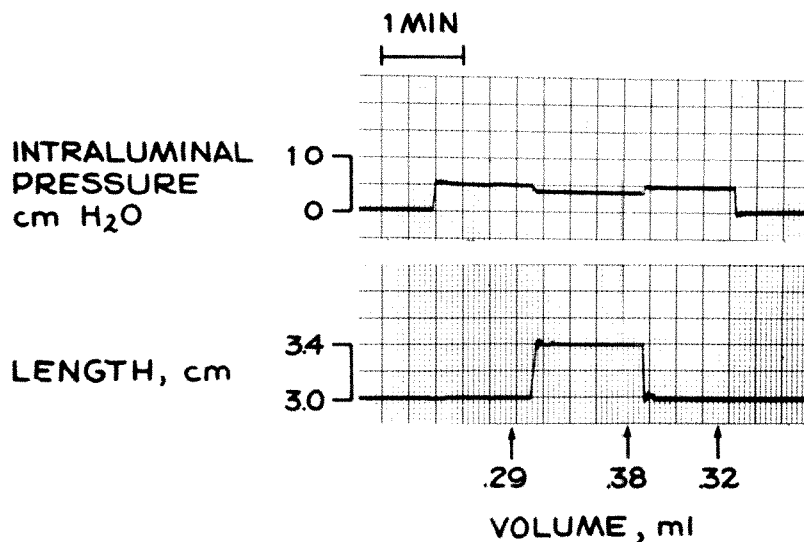


Fig. 7. Dog urethra, *in vitro*. Change in intraluminal volume with mechanical change in length. The recording reads from left to right. The intraluminal pressure is first raised to 5.0 cm H₂O and the volume read at 1 minute. The specimen is lengthened from 3.0 to 3.4 cm and the volume recorded after another minute. The specimen is then shortened back to 3.0 cm and the volume read at the end of the next minute. Finally pressure is reduced to 0 cm H₂O.

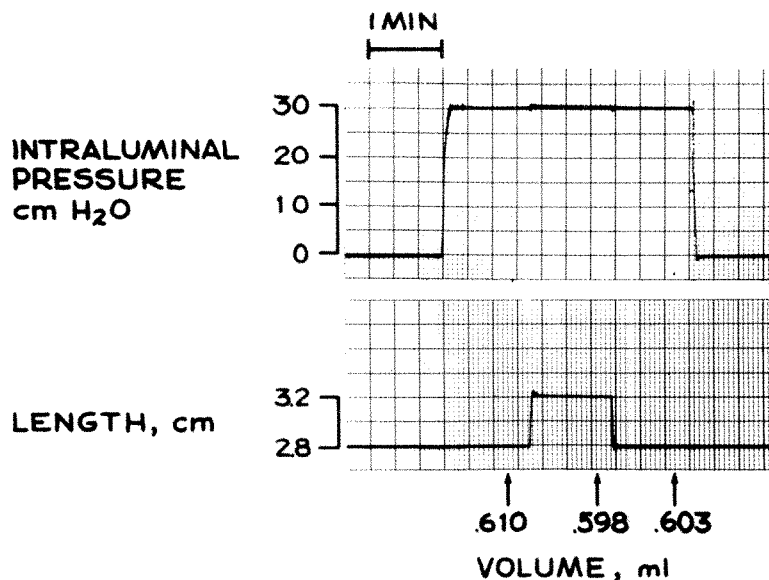


Fig. 8. Latex rubber tube. Change in intraluminal volume with mechanical change in length. The protocol is the same as that in Figure 7 except that the latex rubber tube is filled at 30 cm H₂O pressure.

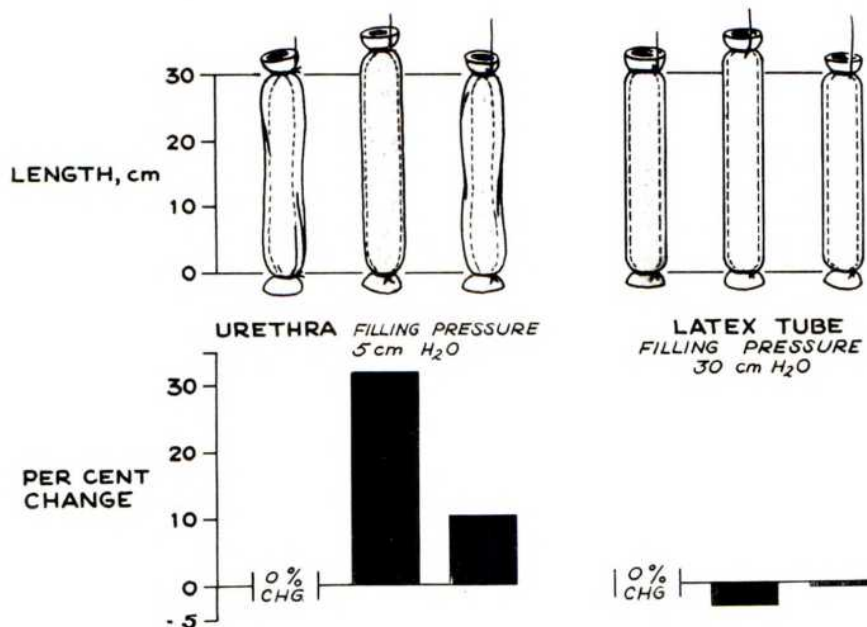


Fig. 9. The different responses of a dog's urethra and of a latex rubber tube to lengthening. At the top, length is illustrated and at the bottom, percentage change in intraluminal volume. The urethra is filled at a pressure of 5 cm H₂O and the latex tube at 30 cm H₂O. The urethra responds with a marked increase in intraluminal volume on lengthening and the latex rubber tube responds with a small decrease in volume. When the original length is restored the original volumes are not entirely restored because of hysteresis.

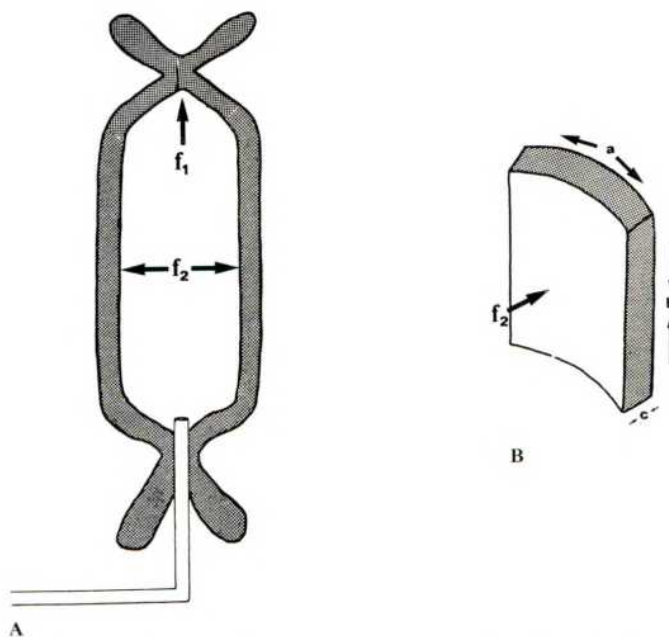


Fig. 10. A, Forces acting on the walls of a closed tube which is subjected to inflation; f_1 tends to lengthen; f_2 tends to widen. B, Forces acting on a block of wall tissue; f_2 increases circumference (a), which produces a tendency of longitudinal (b) and radial (c) contraction.

the urethral specimen or of the latex rubber tube. Thus lengthening of the urethra produces a decrease in reactive pressure, and the reverse occurs in a latex rubber tube.

Discussion

When inflated, the latex rubber tube (constructed of isotropic material) showed no change in length. The explanation for this fact is as follows: a tendency to lengthen, due to an increase in intraluminal pressure (Fig. 10, A) is exactly balanced by a tendency of the wall material to contract in the longitudinal direction because of increase of circumference (Fig. 10, B) (Fenn, 1957). The lengthening of the urethra, in contrast, suggests that the tendency for longitudinal contraction is not proportional to increase in circumference. Another factor may be the difference in wall thickness which is considerably greater in the thick-walled urethra than in the latex rubber tube. However, even when the urethra is inflated near its physiological upper limits, at which time the wall thickness approaches that of the latex rubber tube, considerable lengthening is still occurring.

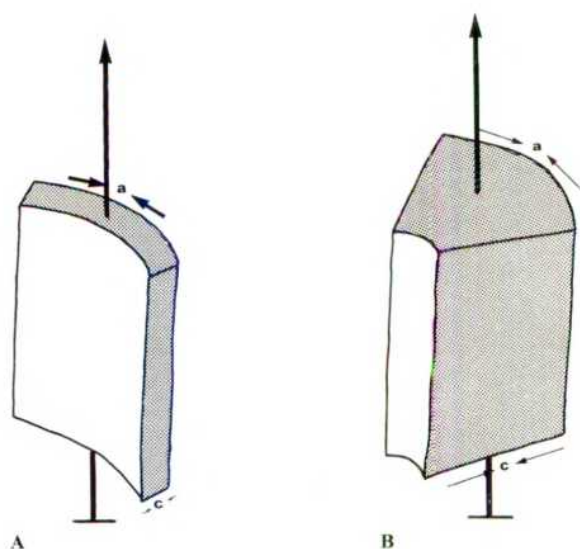


Fig. 11. Forces acting on a block of wall tissue in A, a thin-walled and B, a thick-walled tube, when the tube is mechanically lengthened. Lengthening (direction of large arrows) results in a tendency for circumferential (a) and radial (c) contraction.

The only other factor which might affect the behaviour of the urethra in the organ bath is the amount of longitudinal retraction occurring after removal from the dogs. Yet the amount of retraction was found to be only 4.7 per cent of *in vivo* length on average for all 10 specimens. This amount of shortening was abolished when the specimens were inflated to a pressure of only 5 cm H₂O; thus retraction *in vitro* cannot account for the lengthening produced at pressures above this level. In summary, therefore, the urethra, just like muscular arteries, is anisotropic. It has a tendency to lengthen on inflation, which means that the circumferential elements are stronger than the longitudinal ones.

Mechanical lengthening of the latex rubber tube produced a small but definite decrease in intraluminal volume—which suggests that circumferential tension rises. Figure 11, A illustrates what may happen when a tube is lengthened. If the wall material is isotropic, the tendency for circumferential and radial contraction will be proportional to the amount the tube is lengthened. If the tube is thin-walled, radial contraction will be insignificant, the tendency for circumferential contraction will predominate and circumferential tension will rise. The urethra behaves very differently; intraluminal volume increases when the urethra is mechanically lengthened. Because the wall material is anisotropic, mechanical lengthening must result in a reduction in the tendency

for circumferential contraction, and because the urethra is thick-walled, radial contraction may now produce a significant increase in the size of the lumen (Fig. 11, B). Both these factors may account for the increase in intraluminal volume which occurred when the urethra was mechanically lengthened.

In women, pelvic floor contraction increases the length of the urethra but, if the human female urethra is anisotropic like the dog's, closure pressure will be decreased. Pelvic floor contraction must therefore improve continence by its effect on the bladder neck (Tanagho *et al.*, 1968)—improvement cannot be due to change in urethral wall tension as a result of lengthening. Surgical lengthening of the urethra, as in the Marshall-Marchetti operation, may succeed because it helps prevent permanent funnelling of the bladder neck (Tanagho *et al.*, 1968) and may also position the proximal urethra intra-abdominally, therefore rendering it susceptible to intra-abdominal pressure changes (Enhoring, 1961). Both of these may be responsible for improving continence but are not in themselves related to increase in length.

Summary

The isolated dog's urethra was found to lengthen when inflated, which indicates that the circumferential elements are stronger than the longitudinal ones.

When the urethra was mechanically lengthened, urethral closure pressure was decreased.

Pelvic floor contraction, and vesical suspension operations, which support the bladder base and lengthen the urethra, must enhance continence by their influence on the bladder neck, and not by their effect on urethral length.

Acknowledgement

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Discussion

MR PATRICK SMITH (*Bath*) described a method of urethral lengthening by advancement of the external urethral meatus (Bennett, Mitchell and Smith, 1970) for the treatment of urinary stress incontinence in females. They believed that the success of this procedure was due to the inherent tone of the spiral urethral musculature, which was rendered competent by restoring the normal length of the urethra.

This operation was easily combined with a standard anterior repair though the most impressive results had been obtained in those patients with stress incontinence after a previous repair operation or with a urethrocoele and no vault prolapse.

He thought this urethral advancement combined with a standard repair operation offered a better prospect in the management of stress incontinence.

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A Urodynamic View of Prostatic Obstruction and the Results of Prostatectomy

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The majority of prostatic operations successfully relieve both the outflow obstruction and the patient's symptoms; a critical evaluation of the results however provides no grounds for complacency. Even a simple voiding cystourethrogram performed in a consecutive series of patients after prostatectomy reveals an unexpected incidence of disturbing anatomical results, considering the apparent simplicity of the surgical procedure; these distortions do not, however, necessarily correlate either with the presence or the absence of a patient's postoperative symptoms.

The importance of the composite distal sphincter mechanism in maintaining urinary continence after prostatectomy is well recognised but descriptions of convincing techniques for the avoidance of damage to the intrinsic element of this mechanism during enucleation prostatectomy are few and all too often this precious area of the intrinsic urethral mechanism is merely torn across with the finger incidental to the achievement of enucleation.

Even if the outflow obstruction is efficiently relieved, the distal intrinsic urethral mechanism adequately preserved and the urinary tract sterile, the persistence of an unstable systolic detrusor dysfunction not infrequently compromises the result, causing frequency, nocturia, urgency or impaired control.

Many patients attending a urological department do so as a result of problems which are essentially the result of disordered function; some years ago we set up a separate urodynamic clinic within our departments for their investigation (Turner Warwick and Whiteside, 1969) by synchronous pressure flow cystography (Bates *et al.*, 1970). This has provided the opportunity for a urodynamic re-evaluation of many conflicting concepts and contradictory opinions relating to a wide range of disorders.

In this communication we have attempted to summarise our present thinking on a continuing study of some of the principles underlying the management of prostatic enlargement; in basing this on our own findings we imply no particular originality.

The Response of the Detrusor Muscle to Obstruction

The detrusor responds to chronic outflow obstruction in a variety of functional patterns; it is not clear, however, whether these really represent different reactions to the same condition, different stages in the development of the disorder, or indeed different disorders altogether, but it seems likely that the responses in patients with prostatic enlargement may be more commonly the pure result of superimposed acute mechanical obstruction compared with those associated with bladder neck obstruction in which there may be an underlying element of long-standing detrusor/bladder neck dysfunction (Turner Warwick *et al.*, 1973).

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

Hypertrophy, Trabeculation and High-Pressure Voiding

The detrusor commonly responds to outflow obstruction, irrespective of its cause, by undergoing a global hypertrophy involving the bladder wall and its integral bladder neck mechanism, creating an elevated detrusor pressure and the appearance of trabeculation. True hypertrophy with elevated pressures can also occur in the neuropathic bladder without any element of true outflow obstruction; presumably this is a response to persistent uninhibited detrusor over-exercise between

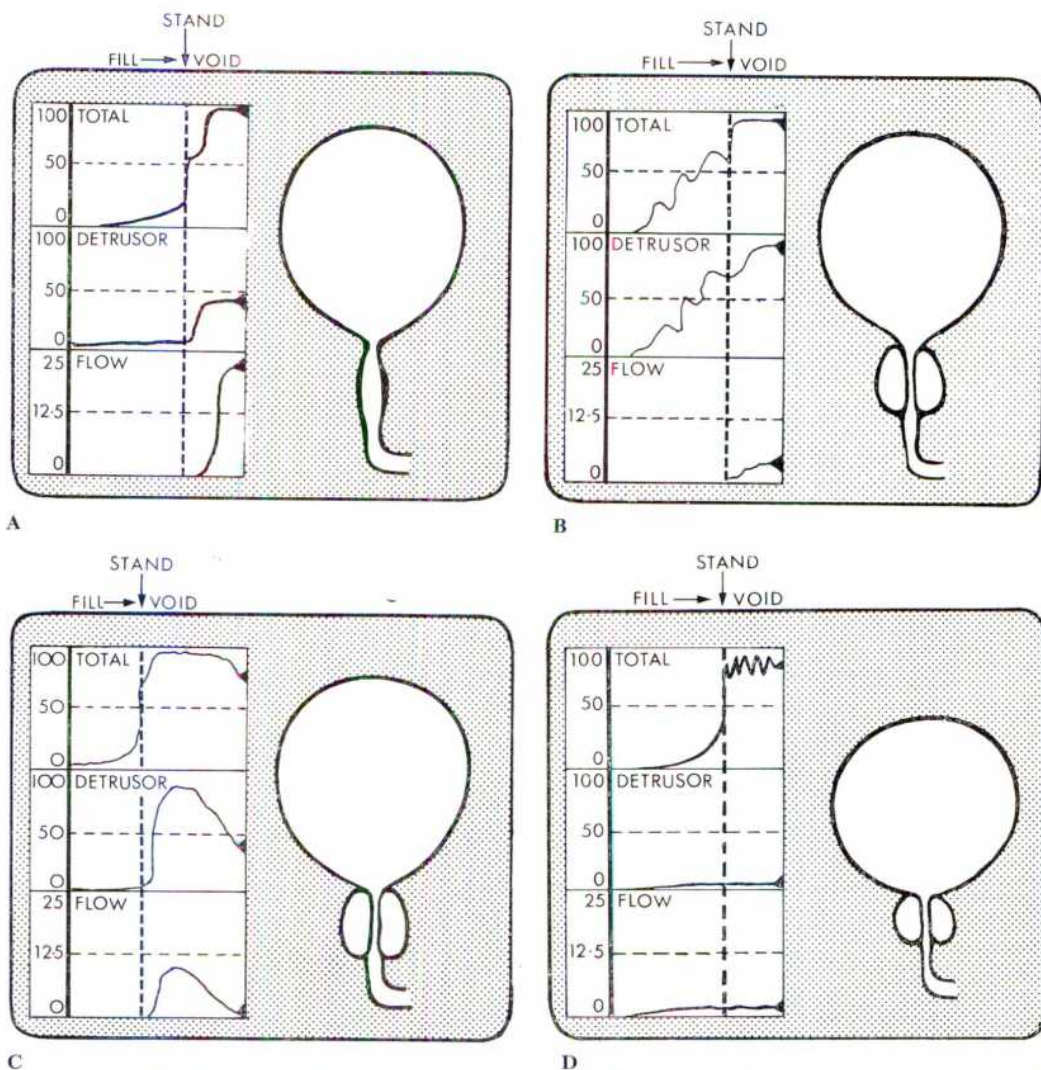


Fig. 1. Pressure-flow-cystography findings in prostatic obstruction. A, Normal. B, Detrusor instability on filling. ? Obstructive ? Neurogenic + Obstruction. C, Detrusor decompensation. D, Low pressure "atonic" detrusor.

voidings. The appearance of trabeculation is not necessarily indicative of detrusor hypertrophy, a raised intravesical pressure or an outflow obstruction, especially in the female.

A common form of voiding pattern associated with prostatic obstruction is illustrated in Figure 1, B. Voiding proceeds at an elevated pressure, the detrusor component of which is commonly in the region of 100 cm water. The normal detrusor pressure in the male is in the region of

50 cm water (Fig. 1, A) but, since voiding efficiency is dependent upon the relation of the voiding pressure to the outflow resistance and the natural variation of each of these is wide, the definition of a precise distinction between "normal" and "abnormal" measurements of either alone may not be very meaningful clinically.

Detrusor Instability: Uninhibitable Detrusor Contractions

In normal circumstances a patient is able to inhibit involuntary detrusor contractions up to the time of intention to void. Detrusor instability is defined as a situation in which the patient is unable to inhibit systolic contractions between voidings; these can be provoked during examination by a variety of innocuous stimuli such as filling (Figs 1, B and 2), passive posture change and coughing, but even greater stimuli, such as the removal of a urethral catheter will not provoke a stable bladder. Some patients develop detrusor instability only under complex higher-centre

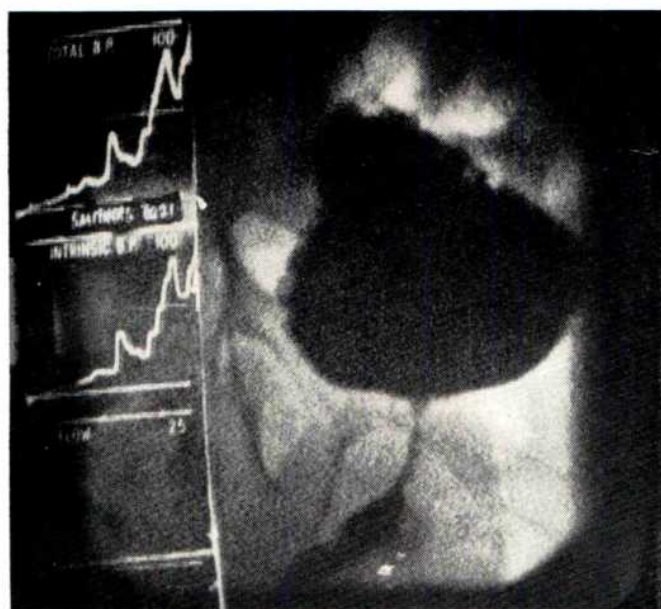


Fig. 2. "Still" frame from video pressure-flow-cysto-urethrogram. Out-flow obstruction; Detrusor instability.

situations such as "giggle incontinence" in girls who usually prove to have stable bladders under the usual conditions of testing and even somewhat hollow laughter.

Instability is sufficiently unusual to regard all forms of it as an abnormality of function until such time as it, and its implications, are better understood.

In general it seems that the important factor in an individual case is whether unstable or uninhibited detrusor contractions occur at all, rather than the actual stimulus that provokes them at the time of a particular test, for this may indeed be different on repeated testing of the same patient (Arnold *et al.*, 1973).

Detrusor instability is dependent upon many factors which influence the excitability in neurological pathways from the cerebral cortex down to bladder wall level; it may be associated with overt neurological disorders but often a neuropathic aetiology may be ill-defined or even entirely presumptive. Detrusor instability may also quite frequently develop in response to simple mechanical bladder outflow obstruction and, unlike most other forms, it is then often reversible, when

the obstruction is relieved. It is perhaps surprising that instability rarely develops in patients as part of the sensory urgency associated with cystitis (Bates, 1971).

Irrespective of our present incomplete understanding of the aetiology and the mechanism of uninhabitable contractions, detrusor instability represents a detectable pattern of bladder behaviour which we feel is better referred to as such, rather than presuming a neuropathy by referring to it as a "neurogenic bladder".

While not all patients with detrusor instability have troublesome symptoms there seems to be a high correlation rate, both ways. It is important however to appreciate that while some patients feel urgency, others have no sensation or awareness of detrusor contractions than the leaking that they may cause.

In the male the distal sphincter mechanism is relatively powerful and it can normally contain unstable detrusor contractions without leakage. If the involuntary detrusor contractions develop a grossly elevated pressure as a result of longstanding obstructive hypertrophy, or if the function of the distal sphincter mechanism is impaired as a result of pre-operative damage or a previous fracture-dislocation injury to the urethra, the resulting post-prostatectomy imbalance may become obvious to the patient and cause a variety of symptoms including frequency, urgency, nocturia and episodic urinary leakage. Detrusor instability in the female is also critical to continence but the reason is commonly different, for it is not so much the pressures involved (which are usually relatively low), but the fact that the detrusor contraction opens the primary defence of the cough-competent and strain-competent bladder neck mechanism and leakage occurs because the distal mechanism of the female urethra is relatively inefficient and unreliable (Turner Warwick, 1970): a similar situation may exist in the male after trans-sphincter urethroplasty for traumatic strictures (Fig. 3, G).

A series of 106 male patients has been assessed in our unit before outflow obstruction-relieving procedures; the majority proved to have detrusor instability according to our tests but the incidence of this did not appear to relate directly to the severity of outflow obstruction (Arnold, 1973); the actual incidence may vary according to the selection of the patients examined.

Although effective relief of bladder outflow obstruction usually results in the resolution of obstructive detrusor instability, this is not invariable. When it persists after operation it commonly results in troublesome symptoms; under these circumstances it is essential to verify that the outflow obstruction has in fact been relieved effectively, whoever performed the operation, for persistent obstruction is a common cause of persistent instability.

Detrusor Decompensation and Low Detrusor Pressure Voiding

Eventually chronic outflow obstruction tends to result in detrusor decompensation and a post-voiding residual urine; residual urine indicates that a degree of decompensation has already occurred as a result of relative imbalance between a particular detrusor mechanism and the associated outflow resistance. Residual urine is not a measurement of the severity of the outflow element nor, conversely, does its absence exclude a significant obstruction (Fig. 5).

Patients with a large residual urine are sometimes labelled as "atonic" clinically but this quite frequently proves factually erroneous; the suspected diagnosis is often considered definitive when a large post-voiding residual persists in the absence of any endoscopically obvious mechanical cause (*e.g.* in females, and in males with an overtly absent bladder neck, prostatic or stricture obstruction). Objective evaluation shows that while some of these patients' bladders may have low-pressure detrusor function associated with a relatively normal outflow resistance, in others the outflow resistance may be unsuspectedly high and associated with a partially decompensated or even a relatively high-pressure detrusor mechanism.

While total detrusor decompensation may be indistinguishable from a low voiding-pressure system in the obstructed state (Fig. 1, D), its commonly partial form is usually recognisable by the detrusor contractions which occur when the bladder is full, but progressively diminish as empty-

ing occurs, leaving the bladder in a hypotonic state with a considerable residual urine (Fig. 1, c). In the absence of overt neuropathy an obstructive detrusor decompensation often recovers following the relief of the obstruction but even if it does not, the oft-quoted hazards of atonic bladder dysfunction following prostatectomy rarely present a problem in the male because, unlike in the female, it is usually possible to establish relatively efficient voiding of a low-pressure detrusor mechanism after prostatectomy by adjusting the outflow resistance of the distal sphincter mechanism with selective sphincterotomy so that the bladder can be emptied on the basis of abdominal straining, comparable to the techniques used to rebalance the outflow resistance after a cystoplasty (Turner Warwick *et al.*, 1967; Turner Warwick, 1973b) which can itself be considered a form of iatrogenic low-pressure detrusor voiding state.

Residual urine after prostatectomy must indicate a degree of residual relative outflow obstruction. If endoscopic review excludes a residual bladder neck, prostatic, or stricture obstruction, it is probable that the site of outflow obstruction lies in the distal urethral sphincter mechanism and, in the absence of a spastic neuropathy involving the extrinsic striated element of this, it is usually the result of a dysfunctional intrinsic urethral mechanism; whether the detrusor pressures prove to be normal or low, the relative obstruction at this site can usually be resolved effectively by selective sphincterotomy with the Otis urethrotome (Turner Warwick and Whiteside, 1969; Turner Warwick *et al.*, 1973). An inadequate transurethral resection quite frequently results in residual apical prostatic tissue and it is particularly important to exclude this before diagnosing a dysfunctional distal mechanism; residual obstructive prostatic tissue localised to this area is a relatively rare early complication after enucleation prostatectomy.

The Mechanism of Prostatic Obstruction

It seems that the main component of prostatic obstruction is simple urethral compression resulting from prostatic enlargement. Although the estimated size of the prostate often appears to be taken into account in making a diagnosis of bladder outflow obstruction the clinical degree of prostatic enlargement is poorly related to the severity of outflow obstruction; nevertheless patients presenting with an incidental finding of gross prostatic enlargement which appears to be causing little in the way of symptoms commonly prove to have a significant obstruction. Although the actual size of an individual's prostate may not be helpful diagnostically it may well be relevant to the clinical management and to the type of surgical procedure that might be indicated should an obstruction be urodynamically proven. If a patient presents with an episode of acute retention a demonstrable degree of underlying dysfunctional or mechanical obstruction is probable; the chances of re-establishing natural voiding after a period of temporary catheterisation are very much less if the prostate is greatly enlarged.

Infection

Residual intra-prostatic infection not uncommonly causes an exacerbation of a pre-existing prostatic obstruction after an episode of urine infection and overtly purulent acinar contents are not infrequently seen during a subsequent prostatectomy. Simple enucleation and transurethral prostatectomy may not, however, reveal or eradicate a posterior prostatovesiculitis and trapped infection in the seminal vesicles may result in recurrent urine infections after a urodynamically effective relief of bladder outflow obstruction; this can be prevented or resolved by techniques involving posterior prostatic resection, vesicular drainage and reconstruction (Turner Warwick, 1969; Turner Warwick *et al.*, 1973).

In general, and perhaps somewhat contrary to clinical expectations, bladder irritation associated with urine infection does not usually seem to create the situation of detrusor instability; the patient's sensations of "bladder spasm" are not usually associated with detrusor contractions and we have noted similar findings in relation to interstitial cystitis.

The Surgical Relief of Prostatic Obstruction

The aim of surgical treatment for prostatic obstruction, by whatever procedure or technique, must be to relieve the obstruction safely and effectively, on a long-term basis, before a significant detrusor dysfunction develops which might compromise the urodynamic result; it must also be accomplished without complications, specifically avoiding damage to the residual sphincter mechanism and the development of strictures at the bladder neck and in the area of the membranous urethra. Any complications, particularly urinary leakage of any degree even for a limited period postoperatively, should always stimulate a surgeon to review his sphincter-preserving technique most critically.

The size of the prostate is commonly taken into account in deciding upon its form of treatment; in considering the management of a "small" prostate the life expectancy of the patient is also important because if a patient develops outflow obstruction at a relatively early age, due to early prostatic enlargement there is a very high probability that this will continue to enlarge and cause re-obstruction, maybe embarrassingly soon, if it is inadequately resected.

Even assuming surgical perfection in these matters, however, the results of prostatectomy are fundamentally dependent upon the subsequent recovery of urodynamic efficiency, which depends upon the recovery of both sphincter and detrusor function.

It is not the purpose of this communication to discuss the relative merits of the various procedures available for prostatectomy, except in so far as they relate to the functional result. By far the most important consideration in this is, of course, the avoidance of damage to the residual sphincter mechanism which is an inherent risk in any prostatectomy.

Isolated Sphincter Mechanisms

Certain routine surgical procedures, including prostatectomy, inevitably result in the ablation of some part of the sphincter mechanism and provide iatrogenic opportunity for the evaluation of isolated sphincter mechanisms (Fig. 3); an understanding of the individual function of these is important to their adequate preservation.

The so-called internal sphincter is better referred to as the bladder neck sphincter. It is normally a cough-competent and strain-proof mechanism. During a prostatectomy the bladder neck is functionally ablated. Attempts to "preserve" it during prostatectomy much more frequently result in an inert mechanism or a secondary bladder neck contracture than a competent bladder neck sphincter, most techniques of prostatectomy involve its definitive ablation in order to avoid these complications. Bladder neck ablation usually represents no disability to the male, apart from reflux ejaculation, because the distal mechanism is reliably competent, provided it has not been compromised either surgically or as a result of previous injury such as fracture-dislocation of the prostate.

The term "external sphincter" tends to focus undue attention on the extrinsic striated muscle surrounding the membranous urethra; in view of its composite nature it is better referred to as the distal sphincter mechanism. In point of fact the extrinsic striated element is, alone, apparently incapable of maintaining continence of urine; it is virtually impossible to damage this bulk of muscle during an enucleation prostatectomy and it is demonstrably functional in patients who are incontinent after prostatectomy, for, while they are able to interrupt their voiding stream with it they can remain dry only momentarily for as long as voluntary contraction can be maintained.

The important element of the composite distal urethral sphincter is the intrinsic urethral mechanism of the membranous urethra and the supramembranous urethra extending upwards through the apex of the prostate towards the verumontanum and lying on the inside of any apical enlargement of the lateral lobes of the prostate that may be present. It is this mechanism which maintains the passive control of urine after prostatectomy (Caine and Edwards, 1958) and

consequently it is this area of the urethra which must be meticulously preserved during a prostatectomy, by whatever technique.

In the course of a radical prostatectomy the proximal half of the intrinsic urethral mechanism (the supramembranous urethra within the apex of the prostate) is resected (Fig. 3, D); furthermore, the residual half of the intrinsic urethral mechanism in the membranous urethra is often compromised by fragmenting it with the anastomotic sutures. Although the bladder neck mechanism may be anatomically "reconstituted" during this procedure, it cannot be relied upon to recover its functional mechanism and it is not therefore surprising that a fair proportion of these patients have a degree of impaired passive urinary control.

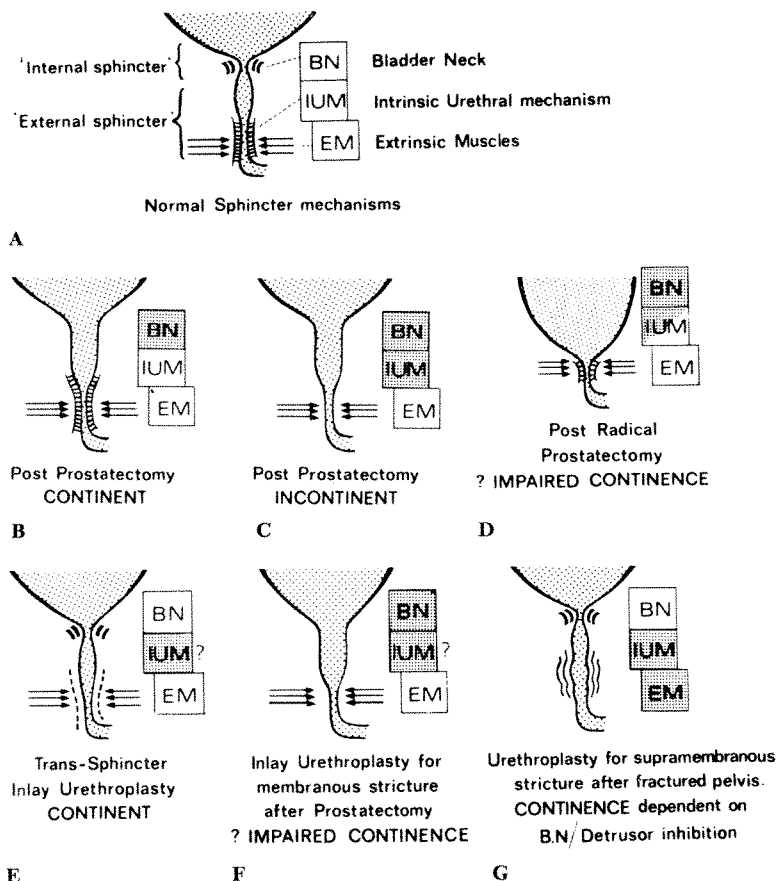


Fig. 3. Isolated sphincter mechanisms after surgical procedures in the male.

In general it seems that a patient requires either an intact bladder neck or an intact distal urethral mechanism to provide reliable passive control over urine. Following a trans-sphincter urethroplasty for total destruction of the distal mechanism resulting from a fracture dislocation of the urethra, the bladder neck can maintain near-perfect urinary control on the basis of detrusor/bladder neck inhibition (Fig. 3, G) (Turner Warwick, 1970, 1973a), provided of course it is not rendered incompetent by unstable detrusor contractions.

After a trans-sphincter urethroplasty for a post-infective stricture involving the intrinsic element of the distal mechanism the patient's urinary control is nearly normal since, in addition to the bladder neck, he has the extrinsic sphincter mechanism which can voluntarily interrupt (as

opposed to voluntarily inhibit) the mid-voiding stream (Fig. 3, c). To perform a bladder-neck ablating prostatectomy on such a patient, or indeed on one who has had a previous non-stricture fracture-dislocation injury to his urethral mechanism, must carry some risk of incontinence. Similar risks apply to the common problem of the patient who has a post-prostatectomy stricture of the membranous urethra because the damage which caused this membranous stricture inevitably compromised the function of the intrinsic urethral mechanism in this area. We are therefore reluctant to advise a trans-sphincter urethroplasty for such a patient, since it may further compromise the function of this mechanism and so risk incontinence; there is, of course, no contra-indication to a sub-sphincter posterior bulbar urethroplasty for an anterior stricture leaving any element of membranous urethral stricture to be treated by dilatation.

It is, however, sometimes necessary to proceed to complete the combined procedure; we have more than 35 patients in our trans-sphincter urethroplasty series who have also had a prostatectomy either before or after it and 7 have impaired control; while this may be fewer than expected, it is too high a risk for an early urethroplasty to be advisable for a relatively simple post-prostatectomy stricture in the membranous urethra if it can be managed easily by dilatation.

Preservation of the Distal Sphincter Mechanism During Prostatectomy

The active area of the intrinsic urethral mechanism of the distal sphincter extends upwards through the apex of the prostate, on the inner surface of any lateral lobe enlargement, diminishing at the level of the verumontanum. Since this active area of the urethra is of vital importance to postoperative continence, a more precise and delicate technique than finger-breaking must be advisable in order to ensure its preservation during enucleation. The most reliable treatment of impaired urinary control after prostatectomy is, and is likely to remain, prophylactic.

A commonly described technique for enucleating a prostate during retropubic prostatectomy involves incision of the anterior capsule and the creation of a plane between it and the "adenomatous" element of the prostate, by blunt dissection and developing this with a finger to achieve circumferential enucleation. The anterior commissure usually remains intact during this procedure; while it may be quite easy to finger-break the apical urethra, it is not always so and it is often divided with a pair of curved scissors passed over the apex of the prostate; this technique not only sacrifices the proximal part of the intrinsic urethral mechanism on the inner aspect of the lower part of the lateral lobes, but it must also to some extent jeopardise the intrinsic mechanism distal to the transection since this is dislocated by the inevitable distraction associated with the development of the apical enucleation plane to the thickness of the finger-tip.

We prefer the teaching of the simple and theoretically safer technique of intra-urethral enucleation of the prostate during retropubic prostatectomy (Turner Warwick, 1969), initiating the enucleation of each lateral lobe in the anterior and posterior sulcus but avoiding any apical enucleation until the urethra has been divided with curved scissors, guided by feel or direct vision, high on the inside aspect of the lateral lobes (Fig. 4) and specifically avoiding any degree of finger-force in this area which could possibly prematurely break across even the most delicate apical mucosa. The small tags of lateral apical urethra created by this technique have presented no problem though gross excess is trimmed; incidentally, the posterior prostatic mucosa and the verumontanum remain intact which is an advantage in the procedure of posterior reconstructive prostatectomy (Turner Warwick, 1969).

Techniques for the preservation of the intrinsic urethral mechanism during a transurethral resection are well described; they include pre-instrumentation internal urethrotomy to reduce the risk of trauma to the intrinsic mechanism during resection by the sheath as a result of gripping by a relatively tight distal sphincter. Nearly all authorities advocate the preservation of the verumontanum as a landmark and stress the importance of the greatest care during the resection of the apical lobes of the prostate since half of the circumference of the intrinsic urethral mechanism is inevitably ablated in any area of the apical urethra through which a loop resects. In order to

remove the apex of the lateral lobes by transurethral prostatectomy it is however inevitably necessary to sacrifice that part of the intrinsic mechanism which overlies the distal apex of the lateral lobes.

At any subsequent transurethral resection there may be an increased risk of damage to the distal mechanism since it may have been partially compromised by scarring from the first procedure. Occasionally the landmark of the verumontanum may also have been resected at the first operation and in these cases it is sometimes helpful to make a new landmark by creating a prominence or "pseudo-verumontanum" initially, in a pre-judged position by appropriate delineating cuts.

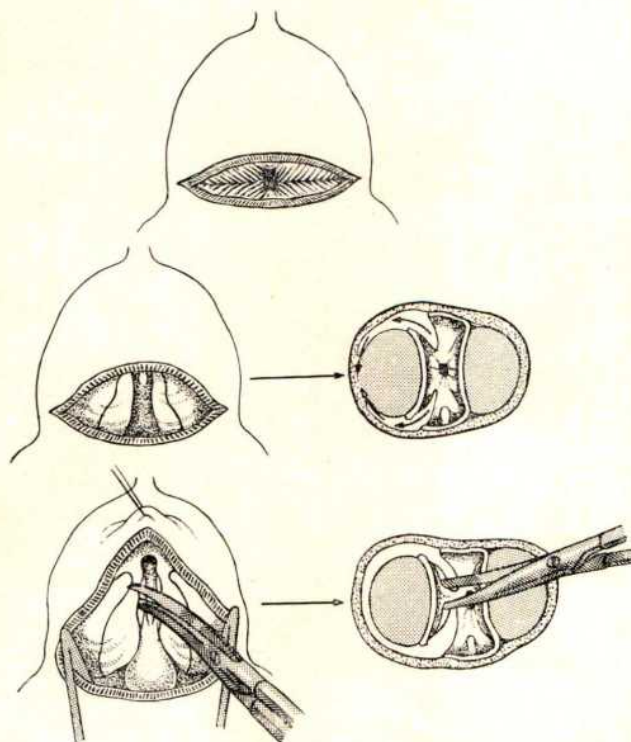


Fig. 4. Preservation of distal intrinsic urethral mechanism. Retropubic exposure of prostate; horizontal incision between upper thirds of prostatic capsule to open prostatic urethra: initial finger enucleation developing anterior and posterior sulci: urethra divided on inner surface of lateral lobes proximal to apex before developing plane of apical enucleation.

The Diagnosis of Obstruction

The diagnosis of well-defined prostatic outflow obstruction, based on symptoms, signs, routine intravenous urography and endoscopy is usually a relatively simple procedure, as is also the decision relating to its management. The exclusion of a significant degree of obstruction and evaluation of mild but important symptoms suggestive of detrusor instability represents a much more difficult problem which cannot be so simply determined. To defer treatment when it is urodynamically indicated, in spite of relatively mild symptoms and clinical signs, may increase the ultimate morbidity but it is of course equally important to avoid operations that are not indicated.

The Significance of a Post-Voiding Residual Urine

The development of a post-voiding residual urine represents a state of bladder failure to compensate for a given outflow obstruction. Arnold (1973) has attempted to correlate the relationship

between outflow obstruction (quantitated by flow rate and pressures) and the volume of residual urine in a consecutive series of patients (Fig. 5). Although a general correlation between the two can be seen there is a significant proportion of patients in the most severely obstructed group who show no excess of post-voiding residual urine.

In general, as will be seen from the objective evaluation of the postoperative complications, there is some urodynamic evidence for advising that bladder-strain to the point of failure should be anticipated and averted rather than awaited. In practice, for many reasons, this is easier said than done because although many patients develop a significant residual urine quite shortly after the onset of their symptoms, others do not.

The development of a post-voiding residual is clearly dependent upon a number of factors, among them the ability of the detrusor to respond in relation to the rate of increase of the outflow obstruction. It is perhaps for this reason that the development of a residual urine tends to occur rather later in bladder neck obstruction since the progressive global hypertrophy resulting from

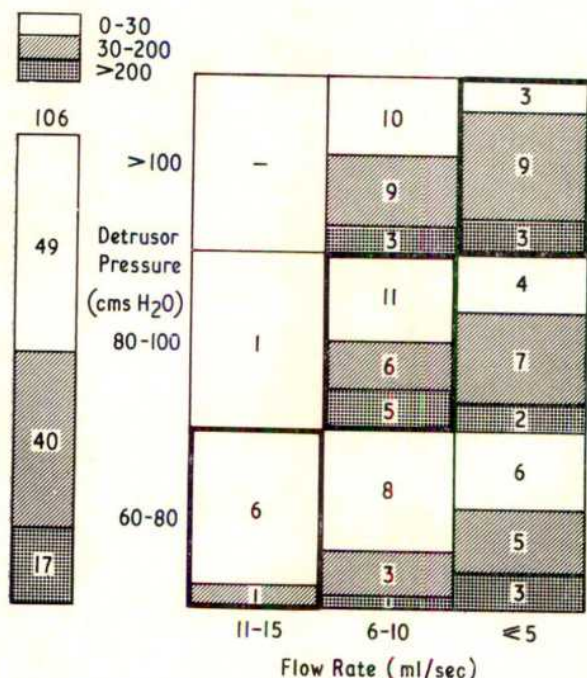


Fig. 5. Residual urine related to severity of prostatic obstruction (Arnold, 1973).

the outflow obstruction may proceed without disturbing the degree of dyssynergic detrusor/bladder-neck imbalance (Turner Warwick *et al.*, 1973); in prostatic enlargement, the degree of prostatic obstruction progresses at its own rate and the sequence of events may depend to some extent on the ability of the detrusor to hypertrophy sufficiently rapidly to compensate for this. While this simple thought may be a relevant generalisation it must again be stressed that there is a wide variety of clinical situations to be explained in relation to various manifestations of bladder outflow obstruction: why some bladders hypertrophy effectively and others do not, why some develop trabeculation, sacculation and diverticula and others do not, why some patients develop a massive residual urine and yet remain virtually asymptomatic. (One of our patients had a 3.6 litre bladder from which he emptied 650 ml at appropriate intervals with normal pressures and flows and with normal bladder sensation, leaving an asymptomatic residual of 3 litres; this patient had no detectable neuropathy, his prostate was only slightly enlarged and a selective

bladder neck incision alone established a urodynamically proven voiding efficiency with no significant residual urine.)

In the present stage of our knowledge we feel that it is more important to analyse the findings than to suggest complex, but no doubt over-simplified and probably spurious, explanations to account for the many variations.

A routine still-film I.V.P. is, of course, an inaccurate measure of dynamic function. In reporting it is better to avoid such statements as "the bladder empties well" for this implies that all is well with the voiding efficiency; it can be accurately stated that it "empties completely" but even this may be misinterpreted by the unwary clinician.

It is fair to state that the absence of residual urine is never an indication that a bladder outflow obstruction does not exist, nor that its treatment can safely be postponed, for it may indeed be absent in the severest degree of outflow obstruction; furthermore, when a significant residual is present, it represents a degree of bladder decompensation and failure which indicates that an appropriate urodynamic appraisal is overdue.

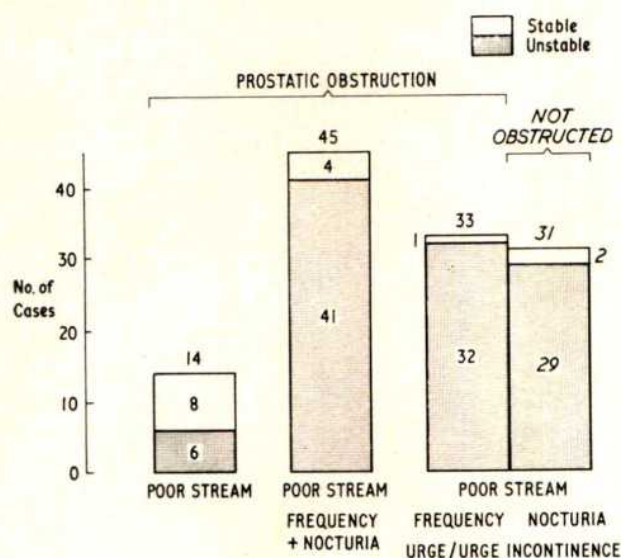


Fig. 6. Symptom groups related to detrusor instability with and without obstruction (Arnold, 1973).

It should therefore be regarded as a cardinal urodynamic rule in the management of prostatic obstruction that prostatectomy should not be postponed simply on the grounds of an absent voiding residual on an intravenous urographic series.

Frequency, Nocturia and Urgency

The symptoms of frequency, nocturia and urgency in the absence of urine infection are very much more difficult to evaluate and there is a high chance that these may indicate a degree of detrusor instability; while this may also be associated with, or be the result of, a significant bladder outflow obstruction, a symptomatic state of detrusor instability can also develop in the absence of any obstruction either as a result of a lifelong instability (not infrequently evidenced by a history of prolonged enuresis in childhood) Whiteside, Arnold and Turner Warwick, 1973), or it may develop quite suddenly and without detectable neurological cause.

Patients complaining of poor stream, frequency and nocturia may or may not have outflow

obstruction: a combination of these symptoms should raise a note of caution since it is obviously important to determine objectively whether or not a true element of obstruction exists before advising surgical relief. Urodynamic evaluation of these patients in our series revealed two groups with identical symptoms (Fig. 6): one of these had bladder outflow obstruction, the other did not: the complaint of a "poor stream" in the non-obstructed group was presumably related to the low-voiding volume associated with frequency. If a real element of outflow obstruction co-exists, its resolution may possibly bring relief; if it does not, then the patient's symptoms are unlikely to improve and may worsen as a result of prostatectomy.

Impaired Voiding Flow

The symptom of increased delay in starting when the bladder is over-distended seems to have a positive urodynamic significance. The patient's estimation of his own stream is often quite accurate in patients with prostatic enlargement since the obstruction is usually superimposed on a previously normal situation, unlike that of bladder neck obstruction which is commonly associated with a lifelong impairment of the voiding stream which the patient may regard as normal for him. Clinical observation of the voiding stream of patients with prostatic obstruction is also less likely to be frustrated by inhibitions of voiding in company but, at best, it is a tedious and time-consuming exercise.

The Voiding Flow Meter

Objective evaluation by a recording flow meter must surely be regarded as an essential screening instrument for every urological department (Fig. 7). An objective record of the voiding flow can be kept in the patient's notes; the patient's opinion of the strength and continuity of his stream, as

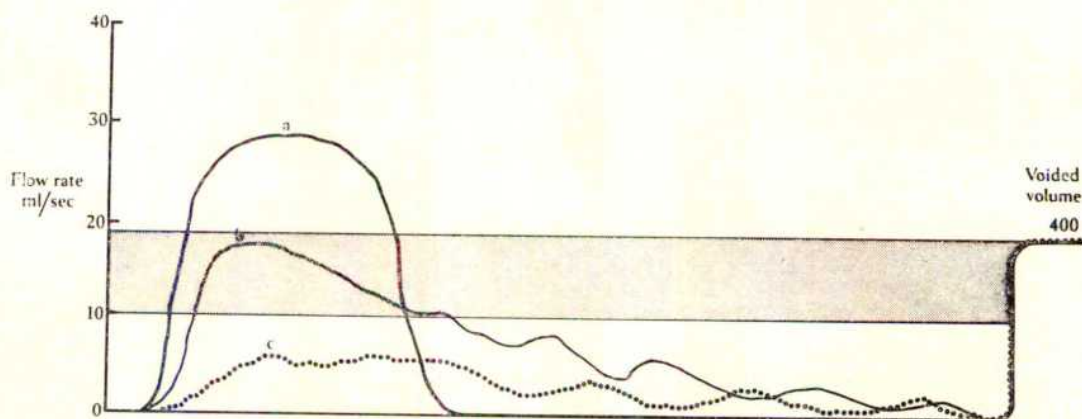


Fig. 7. Voiding flow patterns. A, "Normal" peak flow a "normal" pattern. B, Peak flow in equivocal range; decompensating tail-off. C, Abnormally poor flow.

opposed to changes in it, then becomes largely irrelevant. The excellent or grossly impaired stream is easily recognised and the general shape of the flow rate curve may also be helpful particularly as to whether the flow rate is maintained in the latter part of voiding, or whether it tails off in a variable or intermittent fashion. Helpful as the recorded flow rate curve is, however, it is important to recognise that it is only one of the parameters necessary for evaluating voiding efficiency, and, while it provides essential data, the pattern must not be over-interpreted. A flow rate curve which is equivocal may, for instance, be produced by a bladder developing a high detrusor pressure and thus indicate a significant outflow obstruction while much the same curve, produced

by a low detrusor pressure system might well be acceptable; as with detrusor pressures, it is thus not very helpful to define a precise margin between the normal and the abnormal.

Synchronous Cine Pressure Flow Cystography

The urodynamic data presented in this paper are based upon a synchronous estimation of the total and subtracted detrusor pressure curves superimposed, together with the flow rate curve, on the voiding cysto-urethrographic television monitor, all videotape-recorded with sound track. The details of this technique have been reported elsewhere (Bates *et al.*, 1970); it was developed from the multiple parameter study pioneered by Millar in San Francisco to provide the basic essentials for a clinical routine of urodynamic investigation to which others can be added as indicated. Since the establishment of our urodynamic clinic within the department of urology and radiology at Middlesex Hospital in 1964 we have investigated more than 6,000 clinical problems.

So far as the patient is concerned the 4 parameter investigation does not involve much more than a conventional voiding cystogram; while synchronous record of the various parameters is critical to the investigation of a proportion of clinical situations, once facilities are established there is considerable saving in patient's, physician's, nursing, technician's and instrument time by performing a synchronous investigation as a routine.

Subtracted detrusor pressure evaluation is essential to the certain identification of detrusor instability at the present time, particularly in females, for their detrusor pressures tend to be relatively low and significant changes are often masked on the total bladder pressure estimation, particularly in the erect posture. So far as the investigation of prostatic problems are concerned, the voiding flow, the pressure study and the radiographic studies can if necessary be conducted separately, since the relatively high detrusor pressure changes commonly associated with outflow obstruction in the male are usually identifiable on simple total pressure cystometrogram, especially in the supine position—and therefore at least the proportion of patients whose instability is provoked by simple filling is easily detected.

Voiding cysto-urethrography is, in general, important to the identification of the actual site of an outflow obstruction; it may be difficult to determine from this whether a proximal posterior urethral obstruction is primarily due to the bladder neck or the prostate unless the prostatic urethra is overtly distensible. The voiding cysto-urethrogram is important in locating post-prostatectomy outflow obstruction.

Post-Prostatectomy Symptoms

We have reviewed our findings in 128 patients complaining of symptoms after prostatectomy that have been referred to our urodynamic clinic for evaluation; routine urological investigation was carried out as indicated and those complicated by intercurrent conditions such as diabetes, neurological disorders and simple infection were excluded from this analysis.

11 patients, presenting with a variety of symptoms including frequency, nocturia, burning, perineal discomfort and a feeling of incomplete emptying, proved to be entirely normal on examination and, having been reassured of their normality and convinced by the monitor appearances, 7 of these lost their symptoms completely. This reflects the well-recognised fact that the bladder is often an unreliable witness and requires objective evaluation.

The incidence of the various abnormalities is to some extent a reflection of the selection of patients referred to our clinic. 47 had residual obstruction: 24 due to prostatic residual or re-enlargement, 3 to bladder neck contracture, 6 to urethral stricture and 14 to distal mechanism hypertonia. The relatively high incidence of persistent obstruction after prostatectomy is not an unexpected finding in such a series although it is significant that some of these escaped identification on routine urological examination. Only 13 patients in the series had persistent low-pressure detrusor voiding. Detrusor instability commonly complicated the problem of patients

with persistent outflow obstruction but was present in 42 patients in the series who had no urodynamic evidence of persistent outflow obstruction and this was related to symptoms of frequency, nocturia and urgency.

The analysis of the patients complaining of urge incontinence was particularly interesting since of 45 patients, only 3 appeared to have entirely stable detrusor mechanisms and therefore a pure sphincter type of incontinence; the remainder showed detrusor instability. Again, the incidence of this finding will obviously vary from series to series, but it suggests that detrusor instability is an important factor in a considerable number of patients with postoperative urinary incontinence and one which should perhaps be evaluated in any patient for whom an incontinence procedure is contemplated; without this it would seem difficult to evaluate accurately the various procedures advocated for increasing the bladder outflow resistance.

In general the normal distal mechanism of the male is capable of containing detrusor contractions and maintaining continence and, with the exception of those patients in whom the unstable detrusor contractions create grossly elevated intravesical pressures as a result of a high pressure detrusor response, it is probable that the majority of patients with unstable bladders who have urge incontinence have in addition some degree of distal sphincter damage.

Summary

The responses of the detrusor to obstruction are discussed. Detrusor instability has been a frequent finding and if it persists it appears to be responsible for a considerable proportion of post-prostatectomy symptoms.

A post-voiding residual urine is a clear indication of detrusor decompensation; severe outflow obstruction with high pressure detrusor instability may occur before the detrusor finally decompensates and residual urine develops. The function of isolated sphincter mechanisms is analysed, and a technique for the preservation of the distal sphincter mechanism during enucleation prostatectomy considered.

If further studies prove that detrusor complications, particularly instability, increase as a result of delaying the resolution of a significant outflow obstruction, there are good urodynamic reasons for avoiding them by advising a relatively early resolution of outflow obstruction.

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Treatment of Post-Prostatectomy Urinary Incontinence Using a Silicone Gel Prosthesis

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The principle of providing urethral resistance by compressing the bulbous urethra with an implantable prosthesis derives from the original work of Berry (1961, 1965) in which he proposed that compressing the bulbous urethra with acrylic or silastic blocks might restore continence in the post-prostatectomy invalid. Berry's operation, however, fell into disfavour because of late dislocations of the prosthesis within a seroma about the implant. The wire and other mechanical aids to fixation failed to provide a healing process and the compressing force was ultimately lost in about two-thirds of cases.

Our own early efforts to improve upon the principle of urethral compression were aimed at providing orthotopic vascularised tissue by using the crura of the penis as described by Kaufman

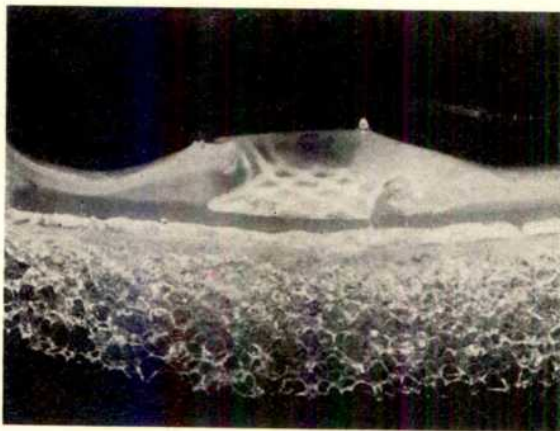


Fig. 1. Cross-section of prosthesis showing external velour of polyurethane, inner capsule of silastic and silicone jelly interior.

(1970, 1972). Although good results were obtained in approximately one-half of cases, the remaining patients either had recurrence of incontinence or developed complications such as urethral strictures or urethral fistulae. Consequently, we reverted to the use of an implantable prosthesis which has the inherent disadvantage of introducing a foreign body, but that possesses the asset of being available in various sizes adaptable to individual perineal anatomy. Furthermore, the prosthesis has certain physical characteristics making it well tolerated and quickly fixed by ingrowth of fibrous tissue. The prosthesis is of ovoid shape with a flat surface on one side and convex surface on the aspect to be applied against the urethra. It is of muscle-like consistency owing to an interior of silicone gel, a capsule of silastic, and an outer velour of polyurethane which acts as a trellis for the ingrowth and fixation by fibrous tissue (Figs. 1, 2 and 3). A further advantage is that it is leak-proof and permits postoperative injection of the capsule to augment its size and compressing force should there be a failure to maintain continence after oedema subsides. The

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prostheses are manufactured in 4 sizes, 2.5 cm × 2.0 cm × 1.7 cm, 3.0 cm × 2.5 cm × 1.7 cm, 4.0 cm × 2.7 cm × 2.0 cm, and 5.0 cm × 2.7 cm × 2.0 cm, and are equipped with 2 veloured dacron straps on either side for the small, medium, and large cushions and 3 straps on either side for the extra large cushion.

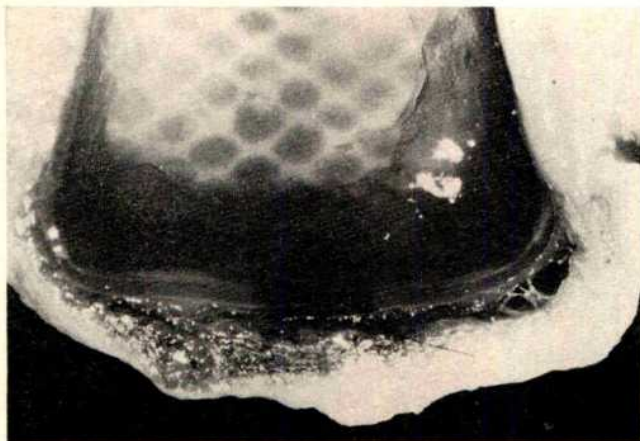


Fig. 2. Section of prosthesis embedded subcutaneously in dog showing dense fibrous ingrowth into velour at 2 months. Note absence of false capsule.

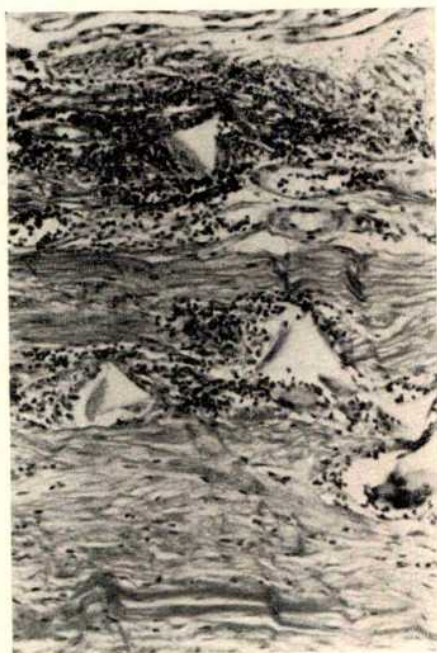


Fig. 3. High power of implanted prosthesis (2 months) showing minimal inflammatory reaction about synthetic material. Note smooth internal lining at bottom. ×150.

Patients and Procedure

Selection of Patients

Patients with post-prostatectomy incontinence following transurethral resection, suprapubic, retropubic or perineal enucleation or following total perineal or retropubic prostatovesiculectomy are generally suitable candidates. Detrusor function should be normal. Patients should not have

urethral strictures because the prosthesis cannot compress a fibrosed bulbous urethra as effectively as the normal urethra and corpus spongiosum. Generally, obese patients do not do as well as others. Urinary infection should be cleared preoperatively.

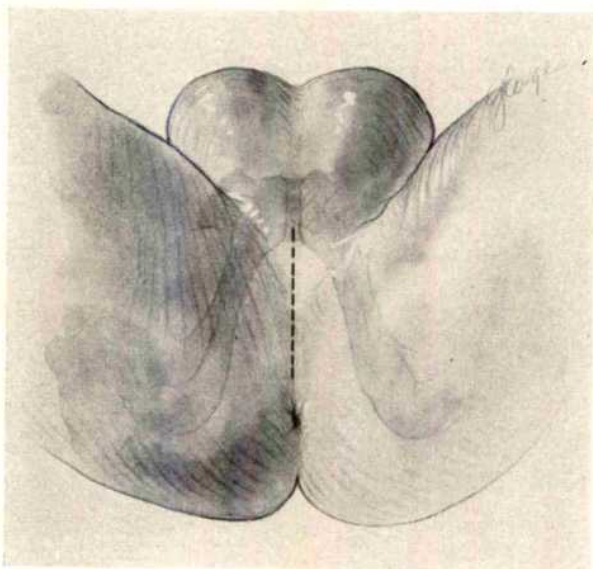


Fig. 4. Drawing indicating placement of incision.

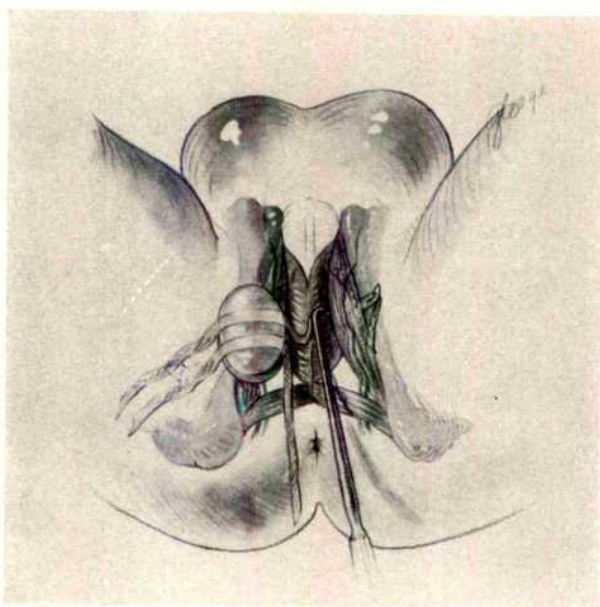


Fig. 5. Drawing showing the placement of the straps about the crura of the penis with a modified ligature carrier.

The operation should be undertaken with reservation in patients with neurogenic bladder dysfunction or in patients who have incontinence following pelvic fractures associated with urethral-prostatic injury.

Patient Preparation

Patients are studied by cystometry, cystoscopy, sphincterometry and cysto-urethrograms pre-

operatively. One day prior to operation broad spectrum antibiotic therapy is begun and is continued for 1 week postoperatively. The genitalia and perineum are prepared with hexachlorophene scrub the night before and the day of operation.

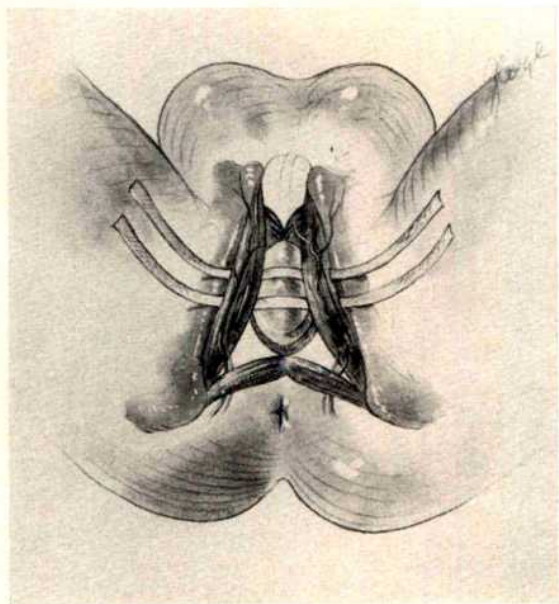


Fig. 6. Drawing showing large silicone gel (2 strap) prosthesis in position.

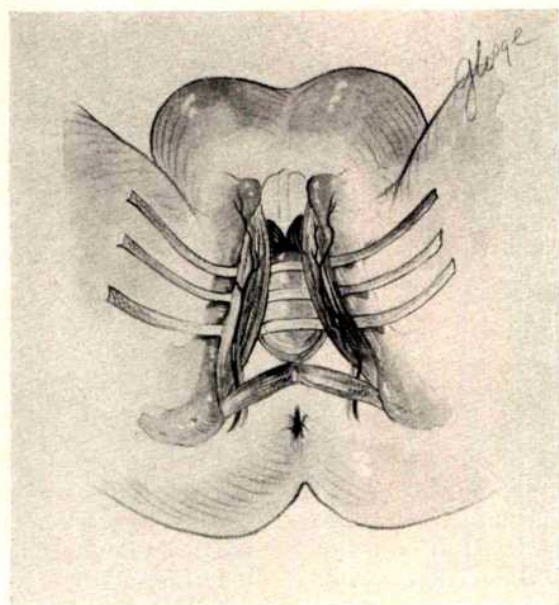


Fig. 7. Drawing showing the extra large (3 strap) prosthesis in position.

Technique of Operation

A midline perineal incision is made, the subcutaneous tissue is sharply incised in the midline, and the bulbocavernosus muscle overlying the urethral bulb is exposed (Fig. 4). An attempt is made to

preserve the longitudinal nerves and vessels that originate from the pudendals, and which run on either side of the bulb. On either side of the bulb the ischiocavernosus muscles can be identified by their white, glistening aponeurotic appearance. The silicone gel prosthesis is prepared by autoclaving (flashing is acceptable) and is soaked in a 1 % solution of erythromycin for 10 minutes. The largest prosthesis that can be accommodated in the perineum is selected because we believe the larger the area of urethral compression the better the resistance effect. Generally the large or extra large cushions are used. The prosthesis is positioned with the convex surface against the bulb. A right angle forceps is inserted bluntly on either side between the crus and its pubic bone and tapes of the prosthesis are pulled through these tunnels. An alternative method is to place the straps in a modified ligature carrier with a sharpened point in the form of a trochar and to place the tape around the crus incorporating a little of the periosteum of the pubic arch in the sweep (Figs. 5, 6 and 7). Bleeding sometimes occurs from the corpus cavernosum, but with compression such bleeding generally stops readily. The straps are then tied loosely over the flat surface of the prosthesis thereby compressing the bulb (Fig. 8).



Fig. 8. Drawing showing straps tied over the flat surface of the prosthesis. The convex surface is placed against the bulbous urethra.

The prosthesis is sometimes injected at the time of operation with saline or a radiopaque medium, particularly if there does not appear to be sufficient compression of the urethra as tested by intra-operative urethral pressure determination. We believe it is best to rely on this means of augmenting compressing effect, rather than depending upon excessive tension in tying the straps about the crura. The latter may lead to necrosis of the crura and urethral erosion.

The subcutaneous tissue is approximated in the midline with absorbable suture material and the skin edges are generally closed with polyglycolic acid continuous subcuticular suture. The wound is sprayed. No drains are used. The 14 or 16F Foley catheter is generally introduced without difficulty after the operation and is left indwelling for 24-48 hours. Patients usually void well after removing the catheter but occasionally the catheter must be reintroduced because of retention. Broad spectrum antibiotic coverage is continued for 1 week postoperatively and sitz baths followed by dry heat application are used several times daily beginning on the second post-operative day.

Results

Between April 1972 and April 1973, 47 male patients were treated for urinary incontinence by insertion of a silicone gel prosthesis. Of these patients, 27 followed transurethral resection of the prostate, 11 occurred after suprapubic or retropubic enucleation, 8 had previous total perineal or retropubic prostatovesiculectomy and 1 had a neurogenic bladder following the removal of a sacral chordoma.

30 patients had not undergone previous operations to correct the incontinence, while 17 patients had had 1 or more previous unsuccessful operations, mostly some type of perineal compression procedure.

Among the patients receiving the silicone gel prosthesis implant as the primary anti-incontinence procedure, 14 were cured, 10 were greatly improved, 2 were moderately improved, and 4 failed to derive benefit. Among 17 patients who had undergone previous unsuccessful operations for incontinence, 5 were cured, 4 greatly improved, 4 moderately improved, and 4 were failures (Table I).

Table I
Incontinence Surgery (March 1973). Silicone Gel Prosthesis

47 Patients	Cure	GI	MI	F
1st Operation	14	10	2	4
30 Patients			6.5%	13.5%
Previous perineal surgery for incontinence × 1 to 4	5	4	4	4
17 Patients	53%		23.5%	23.5%

GI Greatly Improved (wears only a little protective pad).

MI Moderately Improved (wears padding requiring changes × 4 daily).

F Failure (still needs collecting appliance or clamp).

4/5 patients with 2 or more previous perineal operations had only MI (1) or F (3).

In evaluating the results of the operation we have considered patients to be cured only when they are totally continent and need no protection. Patients who are greatly improved wear protective pads for occasional stress incontinence, but are extremely happy with the results. Patients who are moderately improved must wear padding, but previously such patients required a clamp or collecting appliance. Failures denote cases in which the incontinence condition is essentially unchanged.

A theoretical advantage of the appliance is that its self-sealing silastic capsule permits augmentation of its size by percutaneous injection any time during or after the operation. The use of a hyperosmotic solution such as Renografin® or Hypaque® has been most satisfactory in that it will not diffuse through the semipermeable silastic capsule, and is readily visible on X-rays after the injection (Fig. 9).

We have generally practised injection of the capsule when leakage of urine persisted or recurred postoperatively. This is easily done without anaesthesia using a 23 or 24 gauge needle and injecting 3-4 ml of solution at a time. A large capsule will accommodate at least 10-12 ml and the extra large cushion will accommodate up to 16 or 18 ml of fluid. However, we believe that it is better to augment the size of the prosthesis with small increments over a period of months.

25 of the 47 patients required one or more injections during the postoperative period. Among

these cases, 6 were cured, 9 were greatly improved, 2 were moderately improved and 8 patients remained failures even after several injections of the prosthesis.

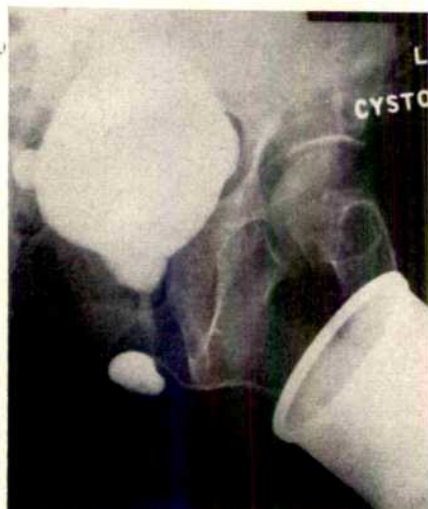


Fig. 9. Postoperative urethrogram showing position of prosthesis injected with opaque medium.

Complications

Among the 47 patients presented, 2 developed wound infections and 4 had persistent draining sinuses. Two of the patients with drainage from the wound were greatly improved and did not wish to submit to removal of the prosthesis with risk of losing their regained urinary control. Two of the patients who developed frank abscesses, however, healed their perineal wounds following drainage of purulent material. This was quite unexpected and attests to the relative lack of tissue reaction caused by this foreign material.

We have encountered 5 patients, 3 of whom were among our own series of implants who developed urethral erosion from pressure of the prosthesis. This will be the subject of a further report. We believe that the straps should not be tied tightly and that this complication is avoidable if this precaution is observed.

Discussion

Not all patients with post-prostatectomy incontinence are suitable candidates for urethral compression procedures. However, the concept of restoring urethral resistance by a long area of compression appears to provide a simple answer to a complex problem for the majority of patients. This is particularly true in patients who are undergoing a perineal operation for the first time since the "pristine" bulbous urethra and its corpus spongiosum are more compressible than is the case when there is stricture or periurethral fibrosis. The major advantages of the silicone gel prosthesis operation are its simplicity, the subsequent option for injection and even the placement of an additional prosthesis *in tandem*. If neither of these modifications brings about the desired result, more complex procedures are still applicable (Tanagho and Smith, 1972; Flocks and Boldus, 1973; Scott, Bradley and Tumm, 1973). The operation is of low-risk with a short period of hospitalisation.

We have previously reported that none of the patients who required postoperative injections of the prosthetic capsule obtained cures (Kaufman, 1973). However, further follow-up of these cases has indicated that it is possible to achieve benefit by injecting the capsule in some cases. In other cases the results of postoperative injection have been disappointing.

Summary

After trials with various urethral compression procedures to restore continence in male patients, an implantable sponge-like prosthesis has been devised which has produced encouraging results in 47 patients followed a minimum of 3 and a maximum of 15 months.

A number of patients have obtained early cures and subsequently lost control. Some of these patients were subsequently improved by injecting the implanted pillow with hyperosmotic fluid percutaneously.

Excellent results have been obtained in 80 per cent of patients who had not been subjected to previous anti-incontinence operations.

53 per cent of patients who had undergone earlier unsuccessful procedures to cure their incontinence were substantially improved or cured after the insertion of a silicone gel prosthesis.

The operation is a simple one with few postoperative complications and we believe that because of these features it deserves further trial as the initial effort to control this disabling iatrogenic problem.

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The Role of Transurethral Prostatectomy in Chronic Prostatitis

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Chronic prostatitis is a diagnosis frequently made in adult males based on clinical findings with few objective laboratory investigations available to support this diagnosis. The clinical features of this condition are diverse. They include recurrent urinary tract infection, discomfort and difficulty during micturition, haematuria and haemospermia, pain in the suprapubic region, penis, perineum, low back and thighs. Perineal and penile pain is often worse after ejaculation and there is consequent loss of libido. The only positive physical sign is severe prostatic tenderness, with palpation per rectum often exacerbating the perineal and penile pain. Currently the laboratory investigation of this condition is limited to the microscopy and culture of the fluid expressed by prostatic massage and its comparison with urethral and mid-stream urine. The aetiology is obscure and many factors have been implicated ranging from sexual excess to sexual deprivation; bacterial, viral, fungal and parasitic infection; auto-immune and psychosomatic disturbance (Grimble and Lessof, 1965; Lennert, Mandorf and Dathe, 1967; Weitzner, 1968; Alyea, 1970; Morrisseau, Phillips and Leadbetter, 1970; Meares and Stamey, 1972). As the aetiology remains a matter for conjecture, so the treatment is not established. In this paper an attempt has been made to define the role of transurethral prostatectomy in diagnosis and treatment of patients with the clinical features of chronic prostatitis.

Patients and Procedures

This study has been carried out on 32 adult male in-patients as part of a wider survey into the aetiology of chronic prostatitis. The age range was 27-74 years with a mean of 53 years, and symptoms had been present for between 9 months and 22 years with a mean of 5 years.

Transurethral prostatectomy was carried out in this group of patients because of failure of conservative measures or because of cystoscopic evidence of bladder neck obstruction.

Urological Investigations

The patients' history, including full details of sexual activities, was documented and physical examination carried out. A full blood count, erythrocyte sedimentation rate, blood urea and electrolytes, W. R., 3 early morning specimens of urine for acid-fast bacilli, chest X-ray and intravenous urography were obtained.

Localisation Studies

Urinary tract localisation studies were performed according to the technique described by Meares and Stamey (1972). The first voided morning specimen was used and collection was supervised at all stages. The first voided 5 ml of urine (VB1) and a mid-stream specimen of urine (VB2) were obtained. Then prostatic massage was carried out and prostatic secretions (E.P.S.) collected, followed by voiding and collection of the next 5 ml of urine (VB3). The 4 specimens thus obtained

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were each divided into 3: 1 for semi-quantitative bacterial culture using blood agar and MacConkey's media; 1 for pus cell counting in a Fuchs Rosenthal counting chamber; the 3rd was submitted to standard virological tissue culture techniques using human embryo lung fibroblasts, HeLa cells and monkey kidney cells.

Psychological Assessment

This was carried out by questionnaire (Goldberg, 1972) using the General Health Questionnaire and the Eysenck Personality Inventory. Patients with chronic prostatitis have been compared with 16 age-matched males admitted for minor non-urological surgery.

Immunology

Serological autoimmune profiles using a standard immunofluorescent technique have been performed on the patients with chronic prostatitis and compared with the profiles of 32 age-matched males from a putative autoimmune population and 27 age-matched healthy male controls.

Endoscopy

The patients were examined under general anaesthesia. A gel containing 2% lignocaine and chlorhexidine was instilled into the urethra and cysto-urethroscopy carried out. The residual volume was measured and a cystoscopic urine sample sent for bacteriology. The appearances of the bladder, bladder neck, prostatic urethra, verumontanum and distal urethra were noted. Transurethral prostatectomy was performed using the Storz resectoscope and a 1.5% glycine irrigating medium. When adenomatous hyperplasia was present and a definite false "capsule" distinguishable, resection was continued to include the inner part of the "capsule" without causing any major perforation. In the absence of hyperplasia, resection was performed cautiously, co-ordinated with rectal examination, to remove as much prostatic tissue as possible. The pieces of prostate removed were divided into 3, every attempt being made to provide for even sampling: 1 sample was immediately fixed in formalin for histology; 1 immediately frozen and stored in liquid nitrogen for subsequent autoantibody and viral studies; the 3rd was used for bacterial culture, the fragments of prostate being inoculated into a Robertson's cooked meat broth medium and incubated for 24 hours. Subcultures were set up aerobically and anaerobically. Postoperatively the patients were maintained on continuous catheter drainage for 24 hours with a frusemide diuresis. Catheters were removed at 24 hours and antibiotics given for 2 weeks according to sensitivities if bacteria were isolated from the E.P.S. or prostate.

Follow-up

After transurethral prostatectomy the patients were reviewed at 6 weeks, and 3 months. Any change in symptoms was noted, and a mid-stream urine specimen was submitted to standard bacteriological examination.

Findings

Histological

The histological appearance of the prostatic tissue from each of the 32 patients has been graded, according to the degree of the chronic inflammatory change present, into 3 groups, mild, moderate and severe. The photomicrographs in Figure 1, A, B and C illustrate the changes in the 3 groups. These chronic inflammatory changes tended to be focal in the mild and moderate groups, but diffuse in the severe group. Benign adenomatous hyperplasia was noted in approximately one-third (12/32) of the cases and was evenly distributed between the groups.

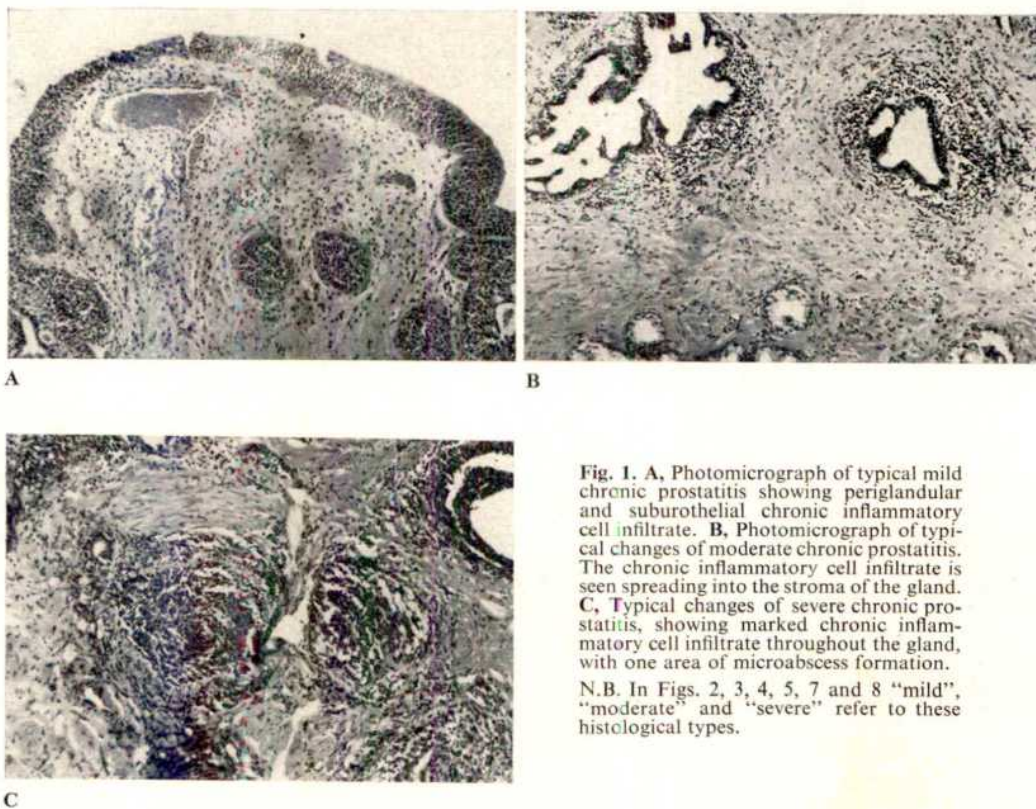


Fig. 1. A, Photomicrograph of typical mild chronic prostatitis showing periglandular and suburothelial chronic inflammatory cell infiltrate. B, Photomicrograph of typical changes of moderate chronic prostatitis. The chronic inflammatory cell infiltrate is seen spreading into the stroma of the gland. C, Typical changes of severe chronic prostatitis, showing marked chronic inflammatory cell infiltrate throughout the gland, with one area of microabscess formation.

N.B. In Figs. 2, 3, 4, 5, 7 and 8 "mild", "moderate" and "severe" refer to these histological types.

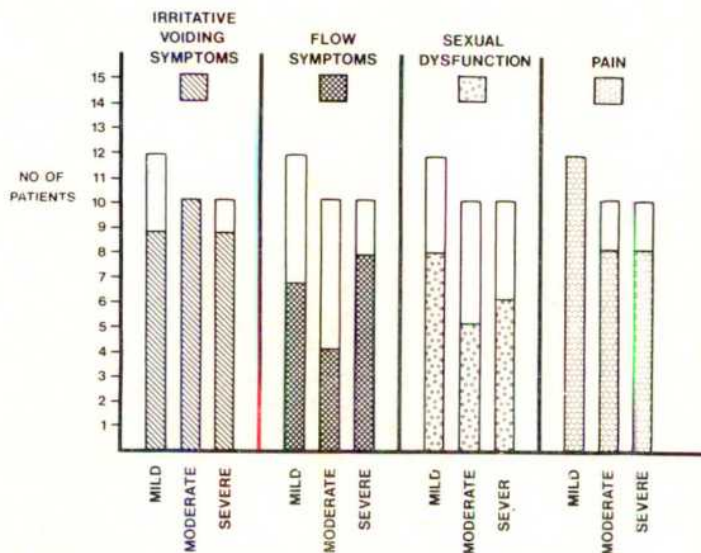
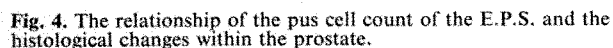
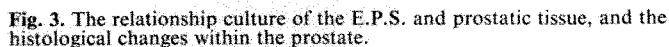


Fig. 2. The relationship of the symptomatology of patients with chronic prostatitis and the histological changes within the prostate.

The majority of patients had irritative voiding symptoms (28/32) and perineal or suprapubic pain (28/32) as shown in Figure 2. Approximately half of the patients complained of diminished stream (19/32) and pain in relation to intercourse with loss of libido, (19/32), Figure 2. Of the 32 patients



there was a past history of venereal disease in 9, a period of catheterisation following spinal surgery in 2, a resection of a vesico-colic fistula due to diverticulitis in 1, and a nephro-ureterectomy for a chronic pyelonephritic pelvic kidney in 1. Cystoscopy had been performed previously in 18 of the 32 patients and 3 others had undergone 1 and 2 previous transurethral resections for chronic prostatitis. Only 6 had received no treatment for their symptoms.

Palpation of the prostate per rectum revealed marked prostatic tenderness in all cases.

Routine urological investigations, excluding cysto-urethroscopy, revealed very few abnormalities. One patient had a mid-stream urine sample with a significant growth of *E. coli* organisms. Intravenous urography showed small solitary bladder diverticula in 2 cases, dilated and tortuous lower ureters in 1 case and bilateral hydroureters and hydronephrosis in 1 patient who had no cystoscopic evidence of bladder neck obstruction. Radiologically obvious prostatic calcification was seen in 4 patients.

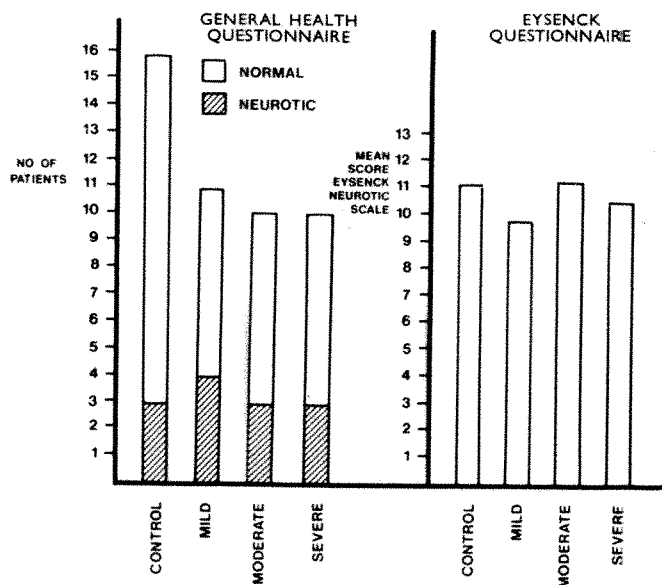


Fig. 5. The results of psychological assessment of the patients with chronic prostatitis by questionnaire, and the relationship with the histological findings.

Localisation

Urinary localisation studies revealed bacteria in the prostatic secretions (E.P.S.) of 12 patients but recognised urinary pathogens in only 5, Figure 3. The pus cell count of the prostatic secretion varied from zero to 108,000 per cu mm, with only moderate correlation with the actual histological changes within the prostate, as shown in Figure 4. Virology of the prostatic secretion was negative in all cases.

Psychological Assessment

Prospective psychological assessment of the patients using the General Health Questionnaire and the Eysenck Personality Inventory shows them to have no greater neurotic tendency than a group of 16 control patients admitted for minor non-urolurgical surgery. Those patients with neurotic tendencies were equally distributed amongst the histological groups as shown in Figure 5.

Immunology

The serological autoimmune profiles of the 32 patients with chronic prostatitis have been compared with 32 age-matched males from a putative autoimmune population and 27 healthy age-

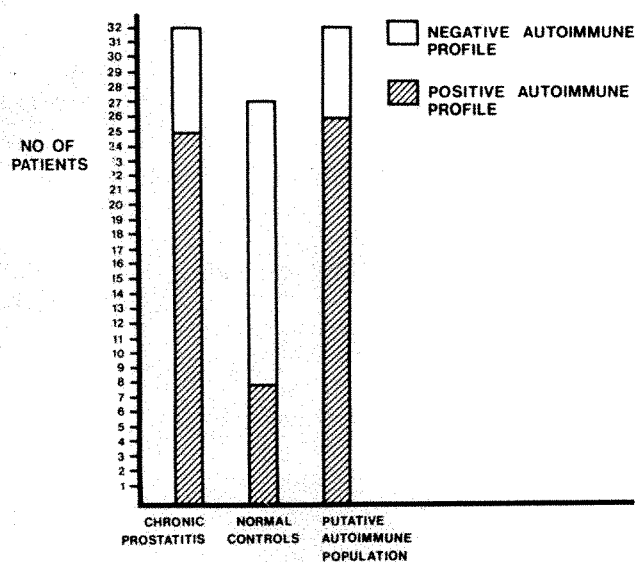


Fig. 6. The serological autoimmune profiles of patients with chronic prostatitis, putative autoimmune disease and healthy controls.

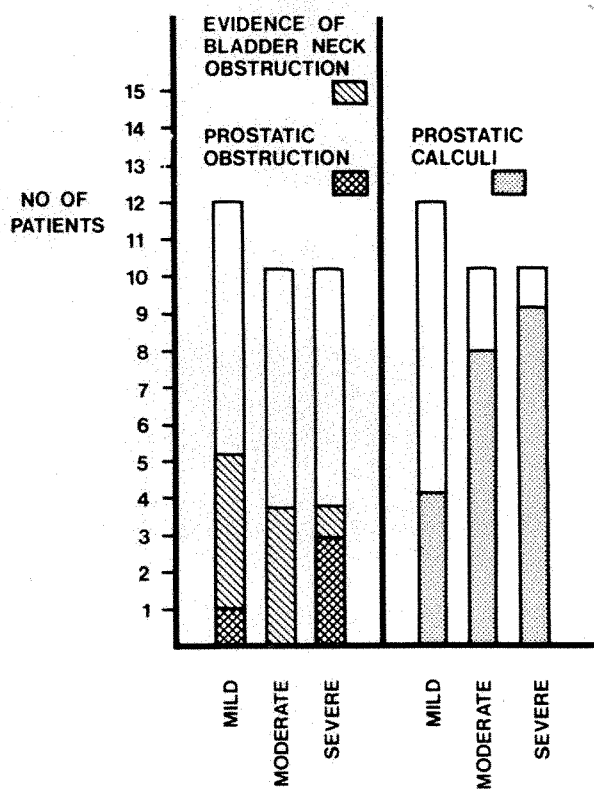


Fig. 7. The relationship of bladder neck obstruction and prostatic calculi to the histological changes within the prostate.

matched males. The number of patients positive for at least one antibody/antigen system have been compared in the 3 groups and from Figure 6 it can be seen that the patients with chronic prostatitis are very similar to the putative autoimmune population ($P = >0.99$) and significantly different from the controls ($P = <0.001$).

Endoscopy

Cysto-urethroscopy revealed no typical features of chronic prostatitis other than suburothelial calculi in the prostatic urethra of 50% of the patients. Bladder neck obstruction was noted in less than half of the cases and prostatic hypertrophy was an infrequent (4/32) cause of obstruction, as shown in Figure 7. Prostatic calculi were noted frequently during transurethral resection and were particularly associated with the prostates showing moderate and severe histological changes of chronic prostatitis (Fig. 7).

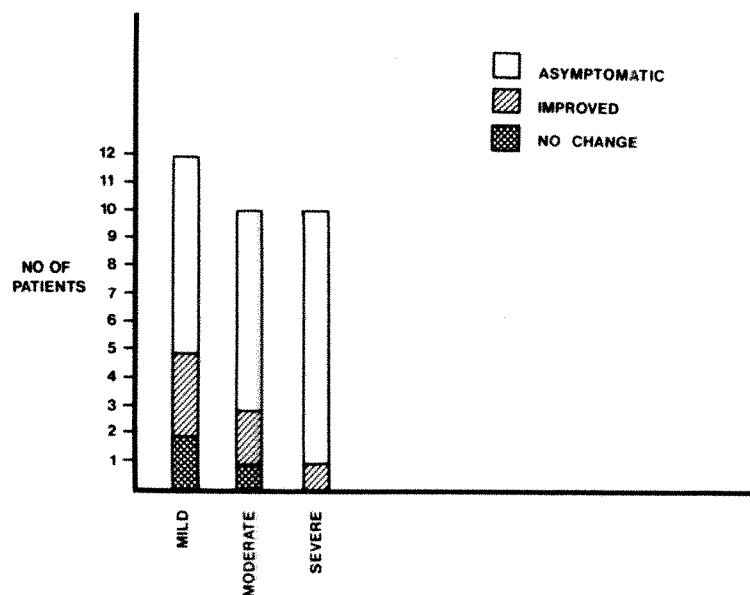


Fig. 8. The results of transurethral prostatectomy for chronic prostatitis, and the relationship to the histological changes within the gland.

Results of Treatment

Assessment of the results of treatment at 3 months shows no mortality, 1 patient with minor stress incontinence and 2 readmissions for secondary haemorrhage requiring catheterisation. 72% of the patients (23/32) have been rendered asymptomatic within 3 months following operation. Of the remainder 6 (19%) have improved and 3 (9%) have observed no change in their symptoms. The most satisfactory results have been obtained in the patients with severe histological changes and the least in the group with mild changes, Figure 8. Of the group of patients undergoing a second (3) or third (2) transurethral prostatectomy, 4 are asymptomatic and 1 has improved. All the patients had normal mid-stream urine at 3 months from operation and no longer required antibiotics.

Discussion

The definitive diagnosis of chronic prostatitis is based on examination of histological material and only when the gland has been radically excised or vigorously resected can this be made with accuracy. Radical prostatectomy carries with it too great a risk of impotence and incontinence to

offer to a patient in the prime of life suffering from a benign disease. Transurethral prostatectomy, on the other hand, in this age group, has no mortality and very little morbidity. In this paper the role of transurethral prostatectomy in the diagnosis and treatment of patients with clinically diagnosed chronic prostatitis has been evaluated. The selection of patients for transurethral prostatectomy in this study was based on the severity of their symptoms, failure of adequate antibiotic therapy and willingness to undergo an operation possibly resulting in sterility but not impotence.

From the evaluation of the histological findings it is clear that all the patients studied had some degree of chronic inflammatory cell infiltrate of their prostate. The significance of mild changes is uncertain as they are frequently seen in prostatic tissue from patients who have no evidence of bacterial infection of the genito-urinary tract (Bourne and Frishette, 1967) and is a common accompaniment of benign hyperplasia of the prostate (Odunjo and Elebute, 1971). There can be no question however that the moderate and severe changes represent an active chronic inflammatory process.

From the data presented in this paper it is clear that it is impossible to distinguish clinically the degree of histological change. Examination of the prostatic secretion (E.P.S.) for pus cells is of only limited use as both false positive and false negative findings are common. The localisation of presumed pathogenic bacteria to the E.P.S. is, on the other hand, diagnostic of chronic bacterial prostatitis (Meares and Stamey, 1972). The role of non-pathogenic bacteria localised to the E.P.S. (*Staphylococcus albus*, diphtheroids, *Micrococcus*), is not clear from this or previous studies (Schmidt and Patterson, 1966). This study supports the view that pathogenic bacteria are responsible at least for the severe histological form of chronic prostatitis. The higher culture rate of bacteria from the prostatic tissue (8/32), compared with the E.P.S. (5/32), illustrates the unreliable sampling obtained with the standard localisation techniques.

The failure to find herpes virus Type 2 or any other virus in this group of patients suggests that viral prostatitis is much rarer than recently suggested (Morrisseau *et al.*, 1970).

The prospective psychological assessment used on this group of patients has failed to detect any greater neurotic tendency in them, when compared with patients undergoing minor non-urological surgery. This casts serious doubts on the validity of previous retrospective studies that have claimed a psychosomatic basis for 50% of cases of chronic prostatitis (Lennert *et al.*, 1967).

The serological autoimmune profile of the patients with chronic prostatitis in terms of the presence of at least one positive antibody/antigen system, closely resembles that of patients with putative autoimmune diseases such as pernicious anaemia, Hashimoto's disease, and the collagen diseases. This strongly suggests that there may be an autoimmune basis to the chronic inflammatory changes seen within the prostate, and further work is required to clarify this aspect of the aetiology of chronic prostatitis.

The role of transurethral prostatectomy in the treatment of chronic prostatitis is undecided. Occasional success has been claimed (Meares and Stamey, 1972) but some authors have advised against endoscopy in chronic prostatitis. This pessimistic attitude is difficult to understand when considered against a background of general acceptance of transurethral resection as the treatment of choice in prostatic abscess, both acute and chronic (Blandy, 1971). The authors' view is that small chronic prostatic abscesses such as have been encountered in this group, cannot be detected by rectal palpation or localisation studies. The alternative methods of treating this disease include prostatic massage, a dubious method of treating any inflamed organ, antibiotic therapy which will usually only suppress symptoms, and radical prostatectomy which has a mortality and considerable morbidity (Meares and Stamey, 1972). The authors would emphasise the need for as complete a resection of prostatic tissue as possible, remembering that in the majority there will be no "false" capsule to act as guide to the limit of resection. Thus 2 or even 3 resections may be required to eradicate all the inflammatory tissue.

The results of prostatectomy in this series, using the patient's appraisal as a means of assessment, compares well with recently published results for transurethral prostatectomy for benign enlargement of the prostate (68.5% very good results and 28.8% improved), (Singh, Tresidder

and Blandy, 1973). Thus it is suggested that the treatment of choice in a patient in whom sterility is not a problem, is transurethral prostatectomy when antibiotic therapy has failed. The patient who wishes to remain fertile continues to be a problem, and suppression of symptoms with antibiotics should be continued until such time as transurethral prostatectomy can be undertaken.

Summary

32 adult males with symptoms and signs of chronic prostatitis have been treated by transurethral prostatectomy.

Preoperative localisation studies have failed to reveal any worthwhile correlation between the pus cell count of the prostatic secretions and the histological changes within the prostate. No viruses were isolated. The incidence of the pathogenic bacteria in the prostatic secretion and the prostatic tissue was increased with the severity of the histological changes.

Psychological assessment by questionnaire showed no greater neurotic tendency in the patient with chronic prostatitis than controls.

The serological autoimmune profiles of the patients with chronic prostatitis were very similar to those of patients from a putative autoimmune population and significantly different from controls, suggesting a possible autoimmune basis for the disease.

There was no mortality, no significant morbidity and within 3 months of the operation 72% of the patients were asymptomatic and 19% improved. These results compare favourably with the results of transurethral prostatectomy for benign enlargement of the prostate. The difficulty of resecting all the inflammatory tissue from a prostate in the absence of benign hyperplasia is stressed and the value of 2 or 3 resections is emphasised.

We wish to thank Dr J. Guthrie, Dr P. Gostling, Dr C. Godber, Dr E. Miller, Mr R. Lloyd and Mr E. Cuthbert for their assistance in this study. We are also grateful to the staff of the Teaching Media Centre, University of Southampton, for preparing the tables and photographs.

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Pharmacological Receptors in the Prostate

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Introduction

The prostate and the urethra are closely related both anatomically and embryologically, and hence it is conceivable that there could be a similarity in their pharmacological response to drugs. Although a vast amount of work has been published on the glandular activities and responses of the prostate gland, relatively little has been written on the pharmacological reactions of its muscular component. Previous *in-vivo* (Raz and Caine, 1972) and *in-vitro* (Raz, Zeigler and Caine, 1972) studies have demonstrated the presence of both α and β adrenergic receptors in the urethra, and the question arose as to whether similar receptors exist in the prostate gland itself. In order to elucidate this point, the following studies were made, using the *in-vitro* isometric technique.

Materials and Methods

A series of 160 experiments were performed on isolated ventral prostate glands removed from mature male rats weighing 200-250 g each. Under ether anaesthesia the ventral prostate gland was carefully dissected from the adjacent tissues, removed and placed in Locke's solution No. 2 at 5°C. Using the same technique as described in our previous papers, the specimens were transferred to Locke's solution at 37°C in a muscle chamber, connected to a force displacement transducer (Grass FT 03C) and Grass recording system, and the isometric responses to adrenergic and cholinergic drugs and blockers were studied. The sensitivity was adjusted so that 1 gram tension produced a pen deflection of 80 mm, and the paper speed was 10 mm per minute.

Results

After a period of 15-30 minutes, the prostate gland was found to exhibit spontaneous muscular activity, characterised by arrhythmic low-amplitude contractions, similar to those seen in the urethra. After this spontaneous activity had appeared, the various drugs were tested, and the following results were obtained.

1. α -adrenergic Agents

Addition of noradrenaline (20 μ g/ml) produced a definite rise in the tone of the prostatic tissue (Fig. 1). This effect was blocked by the prior administration of Rogitine (phentolamine) (20 μ g/ml) (Fig. 2).

2. β -adrenergic Agents

Isuprel (isoproterenol) in concentrations as high as 122 μ g/ml had no significant effect on the basic tone. However, when Inderal (propranolol) was added to the prostate pretreated with Isuprel there was a slight rise in tone, thus indicating that some pre-existing β effect was being blocked (Fig. 3).

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

3. Cholinergic Agents

Acetylcholine (20-40 $\mu\text{g/ml}$) produced an increase in tone, and the further addition of atropine in the same concentration was able to block the above effect (Fig. 4). Acetylcholine had no effect when added to tissue pretreated with atropine (Fig. 5).

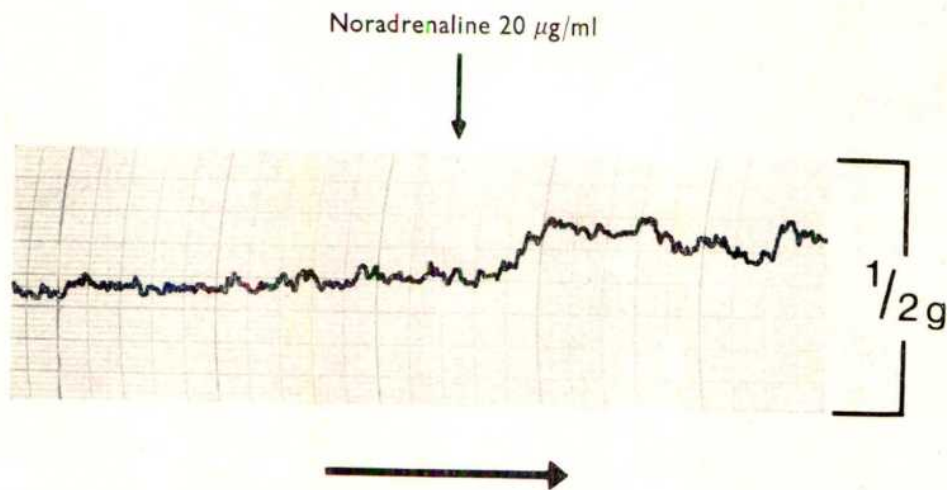


Fig. 1. Rise in tension produced by noradrenaline, an α -adrenergic stimulator.

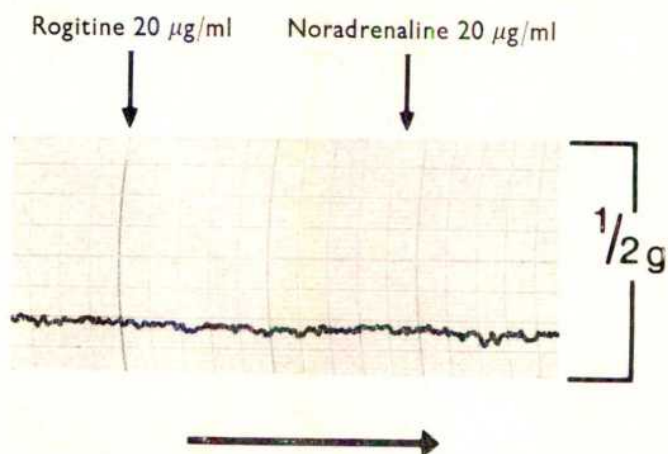


Fig. 2. α -adrenergic blockade by Rogitine prevents effect of noradrenaline.

Discussion

The prostate is composed of glandular, vascular, fibro-elastic and smooth muscle tissue, the latter being responsible for the contraction of the prostate, for part of the closure pressure of the prostatic urethra, and for the spontaneous activity exhibited by the tissue. The muscular activity of the prostate has been rather over-shadowed in the past by the enormous amount of work

that has been done on its glandular activity, but an increasing interest in this tissue component has been developing in the last few years. Fluorescent microscopic studies by Owman and Sjöstrand (1965) have demonstrated a rich innervation with short adrenergic neurones of the muscular tissue in the prostate glands of various mammals, and they have emphasized the marked

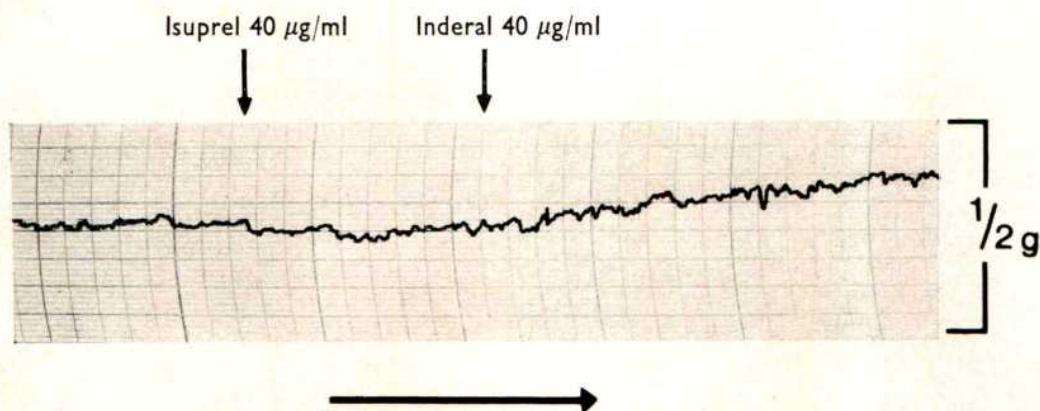


Fig. 3. β -adrenergic stimulation by Isuprel has no appreciable effect, but subsequent β -adrenergic blockade with Inderal results in gradual rise in tension.

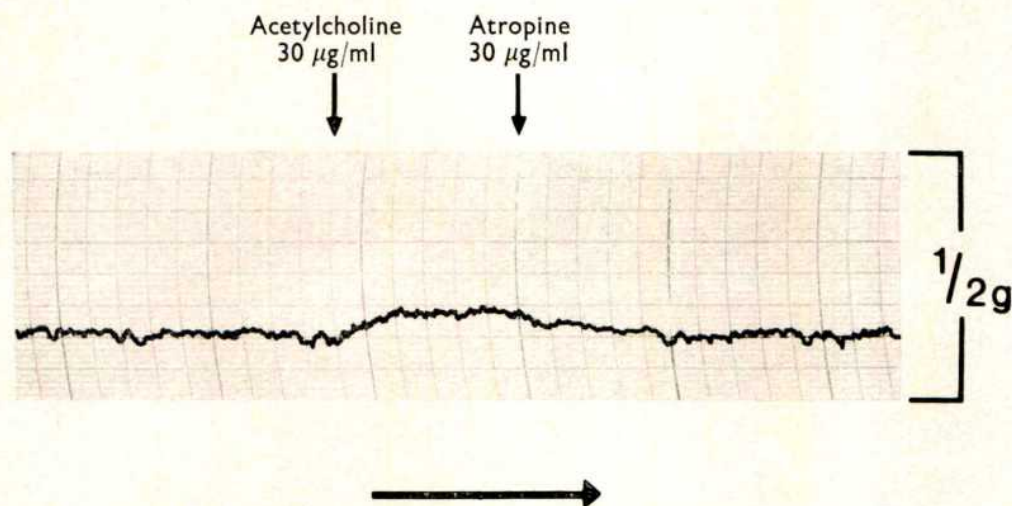


Fig. 4. Response to acetylcholine stimulation, abolished by atropine.

variations that exist in different species. Such findings indicate that one may expect an active sympathetic response by this tissue.

Our present experiments have demonstrated this in a dynamic fashion. They have shown that the tissue examined is rich in α -adrenergic receptors, responding well to α -adrenergic stimulation with noradrenaline. It is notable that this is clearly evident even in the ventral prostate of the rat, in which organ relatively few adrenergic nerve terminals are found, compared with some other species, due to the large amount of parenchymatous tissue and the relatively thin fibromuscular stroma (Owman and Sjöstrand 1965).

For all practical purposes, the experiments show that the β -adrenergic response was so weak as to be virtually non-existent. Cholinergic receptors were found to be present, as illustrated by the responses to acetylcholine and atropine, but this reaction is relatively weak.

The marked response of the prostate to α -adrenergic stimulation may be of clinical interest, with regard to the mechanism of sudden acute retention of urine. Although it is fully realised that species differences in tissue reactions do not permit one automatically to transfer findings in animals to man, preliminary results of similar studies we have been conducting on the human prostate and prostatic capsule indicate that they, also, are richly supplied with α -adrenergic receptors, and respond in a similar manner to the ventral prostate of the rat. It is well known that many patients with benign enlargement of the prostate, who are relatively free from symptoms, may quite suddenly have an attack of acute complete retention, but the medical literature is surprisingly silent regarding the mechanism of such sudden attacks.

If one considers the conditions that are known clinically to cause acute retention in these patients, one finds that they are characterised by a common feature, namely, overactivity of the

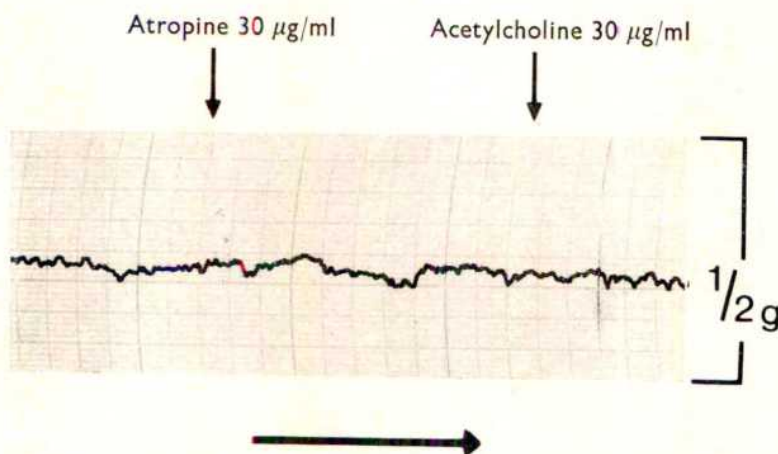


Fig. 5. Lack of response to acetylcholine following prior treatment with atropine.

sympathetic nervous system. For example, overdistension of the bladder due to inability to void for social reasons is frequently the precipitating cause of acute retention in patients with an enlarged prostate; and it has been shown that overdistension of the bladder is associated with increased sympathetic activity, not only in the high paraplegic patient where the reaction is excessive, but also in the normal individual (Taylor, 1963). Similarly, the prostatic patient may develop acute retention as a result of taking medicines containing sympathomimetic drugs such as ephedrine, or as a result of chilling of the body with resultant increased sympathetic activity. We would like to suggest therefore, that at least one of the mechanisms producing acute retention in these patients is the sudden stimulation of the α -adrenergic receptors in the prostate, resulting in a corresponding increase in the intraurethral closure pressure in an already partly obstructed urethra.

Summary and Conclusions

A report is given of a series of experiments designed to investigate the presence of adrenergic and cholinergic receptors in the ventral prostate of the rat.

The results indicate that the organ is rich in α -adrenergic receptors, that β -adrenergic response is negligible, and that cholinergic receptors are present to a moderate degree.

It is suggested that the response to α -adrenergic stimulation may explain the sudden occurrence of acute urinary retention in the prostatic patient.

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Plasma Testosterone: An Accurate Monitor of Hormone Treatment in Prostatic Cancer

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In the 30 years since the original observations of Huggins and co-workers (Huggins and Hodges, 1941), the role of oestrogens in the management of prostatic carcinoma has become well established. There is, however, wide variation in the particular oestrogen agents employed, and in the dosage used, and little is known about the mode of action of oestrogen in prostatic cancer. Because of greater awareness in recent years of the potential cardiovascular hazards of oestrogen administration (V.A.C.U.R.G., 1967), there has been a tendency to employ low dosage stilboestrol therapy, down to as little as 1 mg daily (Bailar, Byar and V.A.C.U.R.G., 1970), or to use alternative oestrogen preparations (Shahmanesh *et al.*, 1973).

There is some experiment evidence to suggest that stilboestrol inhibits prostatic tumour metabolism by direct action on the gland (Farnsworth, 1969) but this is not capable of direct assessment in the human patient, and investigation of the effect of oestrogen administration has therefore been directed at measuring the androgen suppression produced (Alder *et al.*, 1968; Young and Kent, 1968; Mackler *et al.*, 1972). Results published from the Institute of Urology (Robinson and Thomas, 1971) indicated that stilboestrol 1 mg 3 times daily was as effective as larger doses in lowering the plasma testosterone to "female" levels but a recent report has suggested that the smaller dose of 1 mg daily is not fully effective (Kent *et al.*, 1973). Because of the time-consuming nature of earlier methods of measuring plasma testosterone large series of multiple observations have not been possible, but in 1972 Collins *et al.* described a rapid method of radioimmunoassay of plasma testosterone. Since that time, plasma testosterone estimations have been performed in all patients attending the Prostatic Carcinoma Unit of the Institute of Urology, in order to define the minimum effective dose of stilboestrol, and to compare the results with those obtained with alternative preparations.

Patients and Methods

109 patients with carcinoma of the prostate have been investigated. In all cases the diagnosis was established by histological or cytological examination of a prostatic biopsy, and the extent of the disease was assessed by serum acid and alkaline phosphatase estimations, intravenous urography, chest x-ray, skeletal surveys—both radiological and radioisotope using either ^{87m}Sr or ^{99m}Tc polyphosphate—and by cystoscopy and examination under anaesthetic.

18 men of similar age to the patients under study but without prostatic carcinoma were also investigated as controls. These men were all suffering from benign prostatic hyperplasia confirmed by histological examination of prostates removed at operation.

Plasma testosterone was estimated by radioimmunoassay in the Department of Biochemical Endocrinology at the Chelsea Hospital for Women (Collins *et al.*, 1972). In many of the patients serial estimations have been performed, thus providing over 500 separate measurements of plasma testosterone, the majority of which were performed by one technician. In 20 patients, diurnal Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

variation of plasma testosterone was investigated by means of blood samples taken at 6.00 hrs, 12.00 hrs, 18.00 hrs and 24.00 hrs in a single 24-hour period. In all other cases, blood was taken between 10.00 hrs and 12.00 hrs to avoid errors due to the circadian rhythm.

Results

Normal Controls and Untreated Patients

The results in the 18 men with benign prostatic enlargement and in 36 patients with carcinoma of the prostate before starting oestrogen therapy are shown in Figure 1. The patients were divided into 3 groups according to the clinical stage of their disease:

Stage II: tumour confined to the gland with no evidence of local or distant spread.

Stage III: tumour showing local extension but with no evidence of metastases.

Stage IV: tumour with distant metastases.

There was no significant difference in the plasma testosterone levels between any of these groups and the normal controls.

Effect of Stilboestrol and Orchidectomy

The effect of stilboestrol 1 mg 3 times daily in a group of 39 patients studied at various intervals after starting treatment is shown in Figure 2. Within 1 month there was a fall in plasma testosterone from a pre-treatment mean of 280 ng/100 ml to a mean of between 40 and 50 ng/100 ml and this level was maintained for up to 2 years without significant variation.

A comparison of the distribution of results obtained with stilboestrol 1 mg t.d.s. and larger doses is shown in Figure 3. The patients on more than 5 mg daily were maintained on between 10 and 75 mg daily in divided doses. In both groups the mean plasma testosterone was between 40 and 50 ng/100 ml with a peak incidence between 25 and 55 ng/100 ml. In no case did the plasma testosterone rise above 125 ng/ml. Serial results in 5 patients in whom the dose of stilboestrol was lowered to 1 mg t.d.s. because of cardiovascular complications showed that reducing the dose did not lead to an increase in plasma testosterone (Fig. 4).

The results occurring after total orchidectomy are compared with those obtained with stilboestrol 1 mg t.d.s. in Figure 5. Although the peak incidence after orchidectomy was over a narrower range than that on stilboestrol the mean values are almost identical, and the highest value occurring after orchidectomy, 135 ng/100 ml, was greater than the highest result obtained with stilboestrol. Serial observations in 6 patients on stilboestrol 1 mg t.d.s. who underwent orchidectomy indicated no fall in plasma testosterone following operation (Figure 6).

Investigation of the circadian rhythm (Fig. 7) showed that the fall in plasma testosterone achieved by stilboestrol 1 mg t.d.s. was maintained throughout the 24 hours. The effect of 1 mg daily was however less definite. At all times of the day there was wide variation between the individual patients, and in 1 patient of the 7 investigated plasma testosterone never fell below 150 ng/100 ml and for most of the day was above the lower limit of the normal range, 200 ng/100 ml.

Effect of Other Oestrogens

Plasma testosterone levels obtained in patients treated with alternative oestrogen preparations are shown in Figure 8, where these are compared with results obtained with stilboestrol 1 mg t.d.s., and in untreated patients. Honvan 100 mg t.d.s., Premarin 2.5 mg t.d.s. and ethinyloestradiol 0.05 mg b.d. were as effective as stilboestrol 1 mg t.d.s. in lowering plasma testosterone. Investigation of the circadian rhythm in 4 patients on Honvan 100 mg t.d.s. and 4 on Premarin 2.5 mg t.d.s. indicated that the suppression of plasma testosterone produced by these agents was maintained throughout the 24 hours. Premarin was not fully effective in a dose of 1.25 mg t.d.s. and TACE (tri-p-anisylchloroethylene) had no detectable effect on the plasma testosterone level.

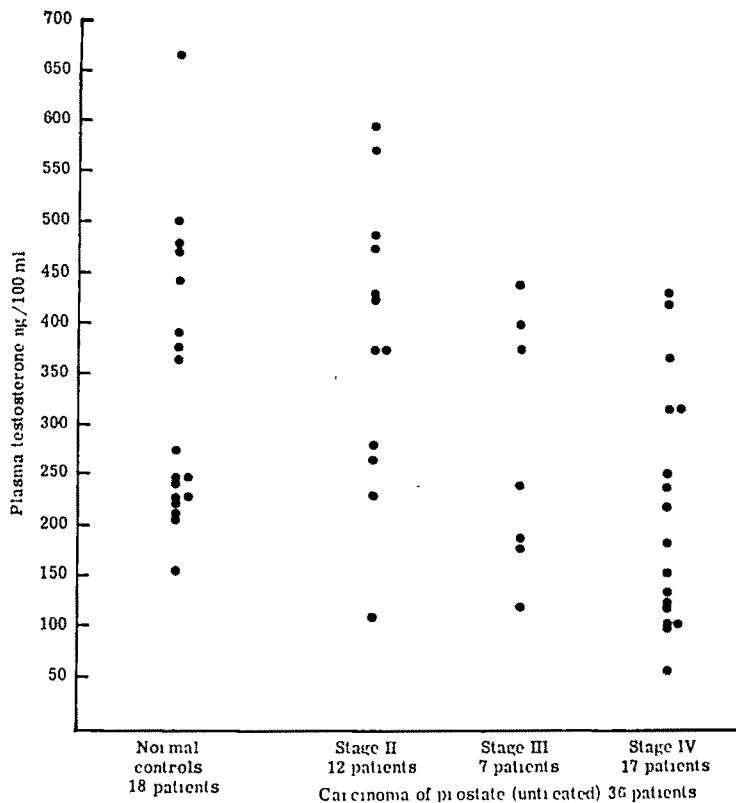


Fig. 1. Plasma testosterone levels: normal controls and prostatic cancer before treatment.

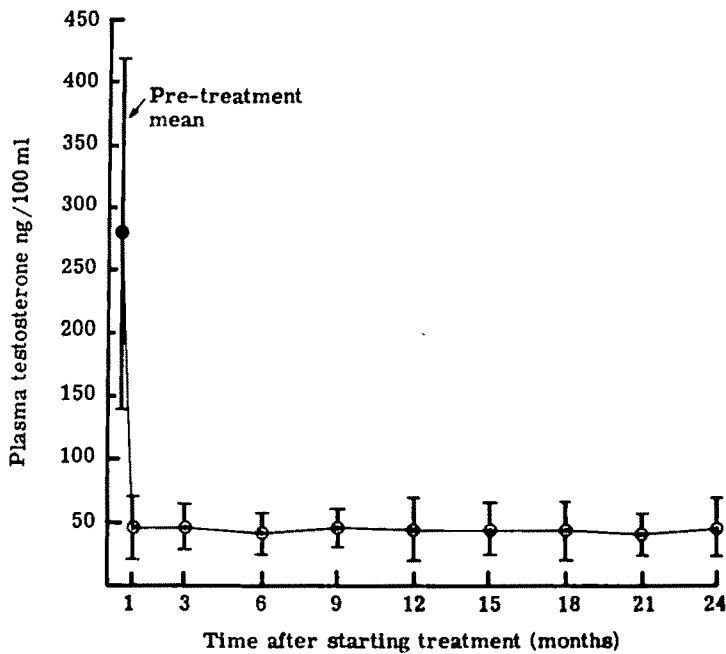


Fig. 2. Plasma testosterone (mean $\pm$ S.D.) in 39 patients, up to 2 years after starting treatment with stilboestrol 1 mg t.d.s

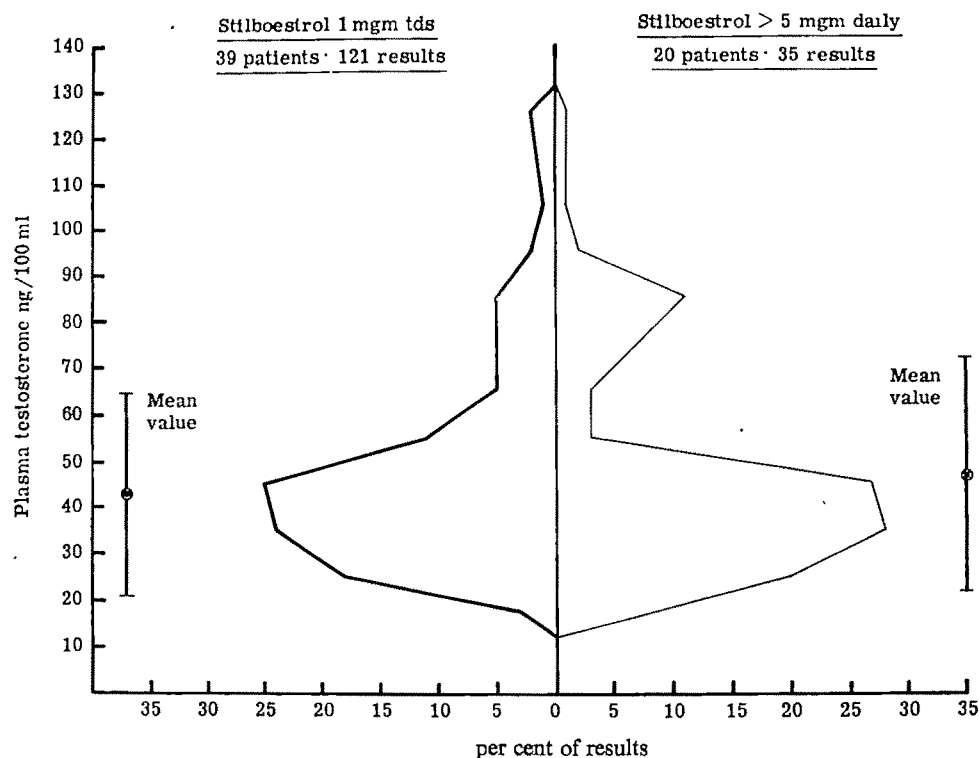


Fig. 3. Distribution curves (with mean $\pm$ S.D.) of plasma testosterone levels: stilboestrol 1 mg t.d.s. and >5 mg daily.

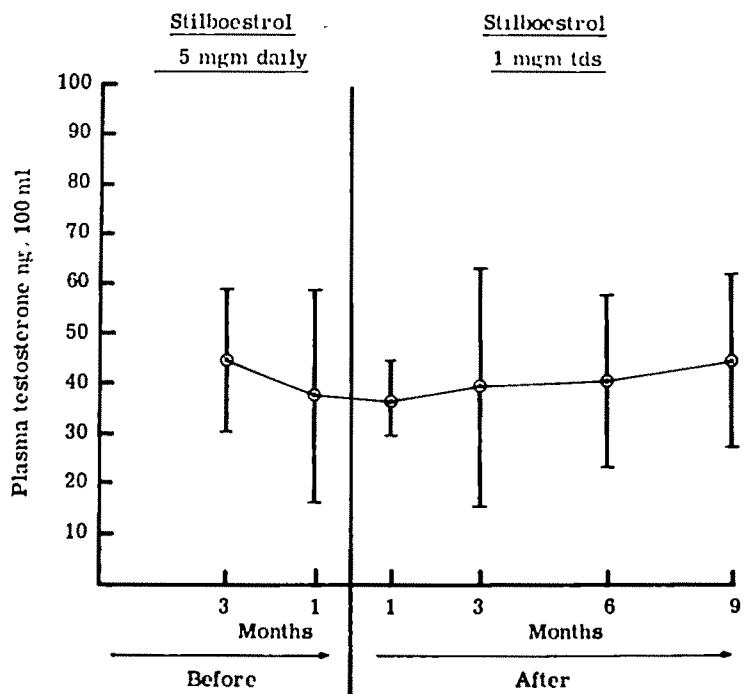


Fig. 4. Plasma testosterone (mean $\pm$ S.D.) in 5 patients before and after reducing stilboestrol dosage.

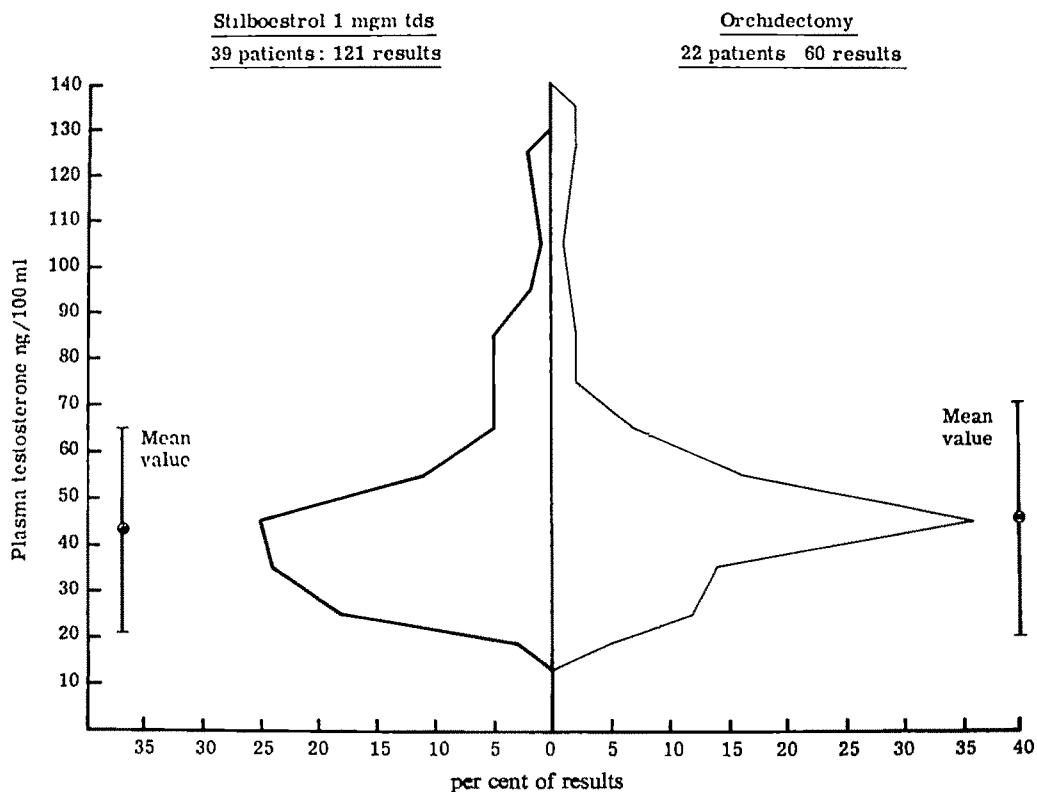


Fig. 5. Distribution curves (with mean $\pm$ S.D.) of plasma testosterone: stilboestrol 1 mg t.d.s. and orchidectomy.

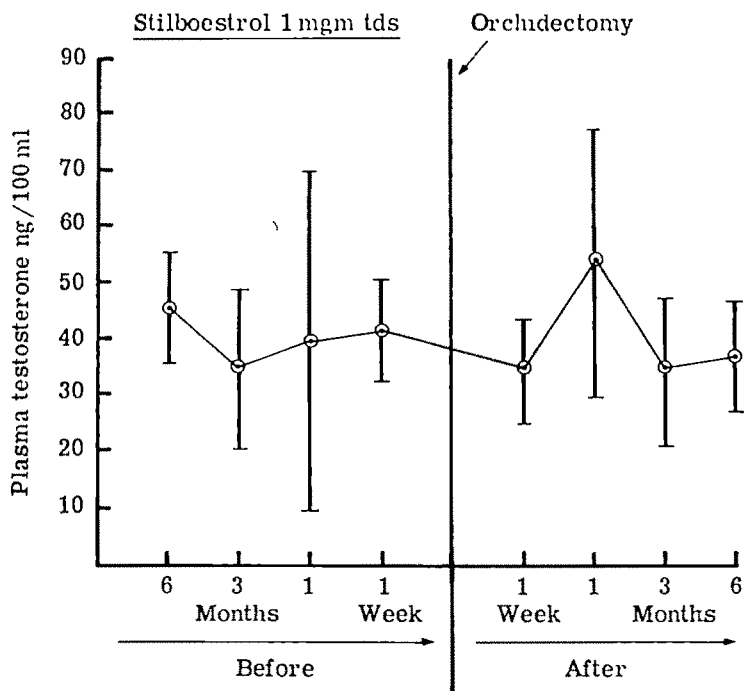


Fig. 6. Plasma testosterone (mean $\pm$ S.D.) before and after orchidectomy, in 6 patients on stilboestrol 1 mg t.d.s. up to time of operation.

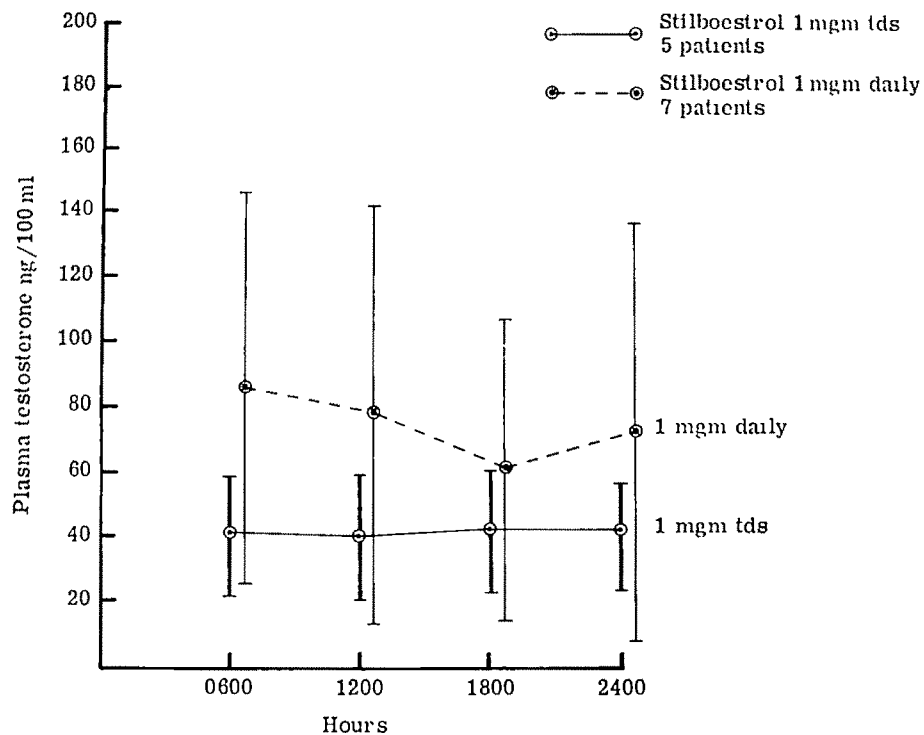


Fig. 7. Diurnal variation of plasma testosterone, comparing the effects of stilboestrol 1 mg daily with 1 mg t.d.s.

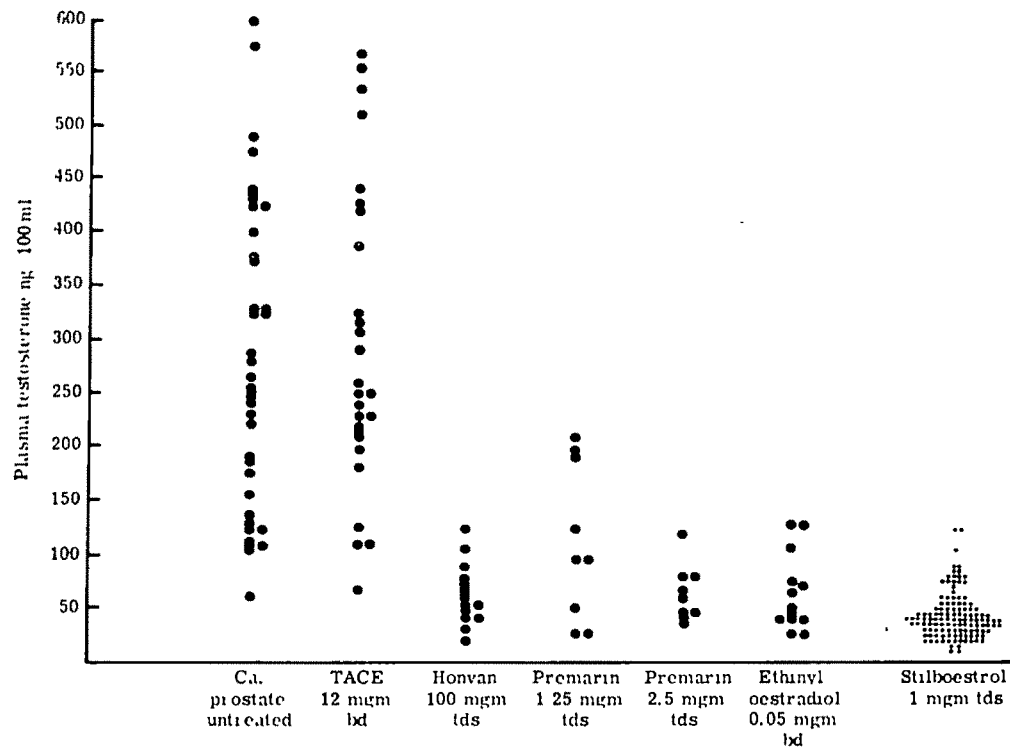


Fig. 8. Effect of alternative oestrogen preparations on plasma testosterone.

Adrenal Suppression and Pituitary Ablation

Patients who failed to respond clinically to treatment with oestrogens or orchidectomy, or who "escaped" from hormonal control, were treated either by suppression of adrenal function with aminoglutethimide, an anticonvulsant which inhibits steroid synthesis (Hughes and Burley, 1970), or by ablation of the anterior pituitary by yttrium-90 implantation. Figure 9 shows the mean plasma testosterone levels obtained in these patients, compared with stilboestrol 1 mg t.d.s. Serial studies in 7 patients subjected to pituitary irradiation showed a marked drop within 1 week of implantation of yttrium (Fig. 10) but no such fall in plasma testosterone occurred after administration of aminoglutethimide.

Discussion

Over 20 years ago it was said of oestrogen therapy in prostatic carcinoma: "there is no other commonly used principle of therapy whose method of application varies as widely" (Smith, Rush and Evans, 1951). It is only recently that such variation has become susceptible to objective clinical assessment by the measurement of the hormone response; assessment of any direct effect on the prostate itself remains in the future. Our investigations indicate that stilboestrol is as effective in lowering plasma testosterone in a dose of 1 mg 3 times daily as in larger doses, and since clinical response does not seem to be impaired at the lower dose there is no rationale for administering stilboestrol in any greater amount. On the other hand, the hormone response to 1 mg daily is not as uniformly demonstrable, and further investigation of this and intermediate doses is needed. It is claimed that Premarin has less cardiovascular side-effects than other oestrogens, and, as it is equally as effective as stilboestrol in lowering plasma testosterone, further investigation and trial of this preparation may be of value. The means by which TACE exerts its effect on carcinoma of the prostate remains obscure since it produces no fall in plasma testosterone, and the testes of 3 patients treated with TACE followed by orchidectomy showed active spermatogenesis.

We have found no evidence to suggest that exacerbation of disease is accompanied or preceded by a rise in plasma testosterone, but the fact that further interference with the hormonal milieu, by either pituitary irradiation or administration of aminoglutethimide, is followed by a 60-70% symptomatic improvement in patients with relapse (Fergusson and Hendry, 1971; Robinson, Shearer and Fergusson, 1973), suggests that these tumours are able to utilise for their metabolic needs either the very small amounts of circulating testosterone still remaining or alternative sources of hormone (Hollander, 1963; Farnsworth, 1970), rather than that they are truly hormone-independent. Our failure to demonstrate a fall in plasma testosterone with aminoglutethimide is at variance with earlier studies using a different method of measuring plasma testosterone, which indicated that such a fall may occur (Robinson and Thomas, 1971).

Conclusions

Estimation of the plasma testosterone provides a reliable objective measure of the effects of oestrogen therapy in prostatic cancer. It suggests that "female" levels of circulating testosterone are as easily achieved with low doses of stilboestrol as with high doses, and that oestrogen administration has the same effect on circulating testosterone as extirpation of the testes. Other oestrogens, with the exception of TACE, are as effective as stilboestrol but the effectiveness of very low dose stilboestrol (1 mg daily) remains open to question. Phosphorylated stilboestrol (Honvan) is no more effective than diethyl-stilboestrol in suppressing testosterone secretion, and since when administered orally it is probably dephosphorylated before absorption, there seems little indication for its continued administration by this route.

Such testosterone as remains in the plasma in spite of adequate testicular suppression by

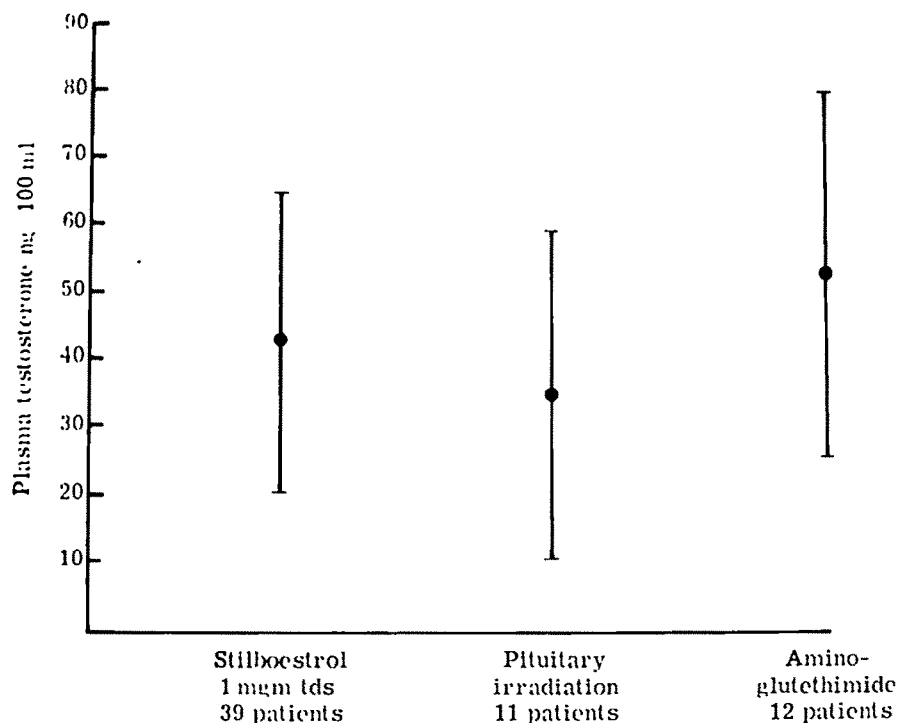


Fig. 9. Plasma testosterone (mean $\pm$ S.D.): stilboestrol 1 mg t.d.s., after pituitary irradiation and on aminoglutethimide 250 mg q.d.s.

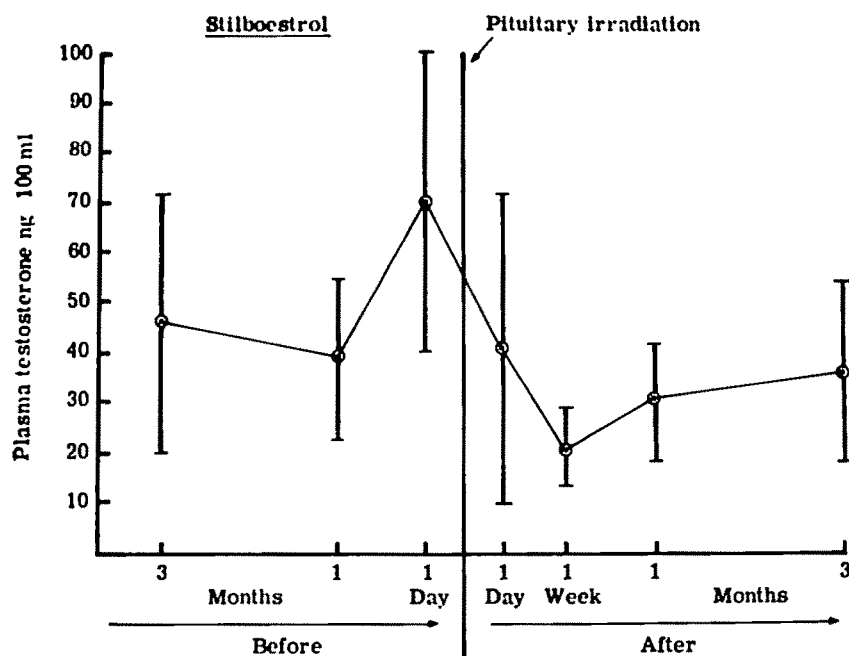


Fig. 10. Plasma testosterone (mean $\pm$ S.D.) in 7 patients, before and after pituitary irradiation.

oestrogen presumably originates from the adrenal and this provides a rational basis for attempts to control the "hormone-resistant" tumour by modifying adrenal function. This contention is supported by the fall in plasma testosterone found after pituitary ablation.

Summary

Plasma testosterone has been estimated by radioimmunoassay in 109 patients with prostatic carcinoma and 18 men of similar age with benign prostatic hyperplasia.

Stilboestrol 1 mg 3 times daily, Premarin 2.5 mg 3 times daily, Honvan 100 mg 3 times daily or ethinyloestradiol 0.05 mg twice daily are as effective as large doses of stilboestrol or as orchiectomy in producing a profound and sustained fall in plasma testosterone, but stilboestrol 1 mg daily is not uniformly effective.

TACE has no measurable effect on the plasma testosterone.

No rise in plasma testosterone is noted in relapse, but pituitary ablation by implantation of yttrium-90 produces a fall in plasma testosterone greater than that achieved by oestrogens alone.

We thank Mr M. D. Mansfield, Chief Technician in the Department of Clinical Endocrinology at the Chelsea Hospital for Women, London who personally performed most of these investigations, and Mr J. P. Williams, sub-dean of the Institute of Urology and Mr J. C. Park, Consultant Urologist, Greenwich District Hospital, London, who referred many of their patients to us for investigation. We are indebted to Miss F. Wadsworth and Mr R. E. Bartholomew of the Departments of Medical Art and Photography of the Institute of Urology for their help and advice in the preparation of the charts and Miss Valerie Filler who prepared the typescript. This work was supported by the St Peter's Research Trust.

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The Relationship between the Urethral Flora and Urinary Infection in the Catheterised Male

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It is now more than 10 years since the introduction of closed systems of catheter-drainage for the prevention of catheter associated urinary tract infection (Pyrah *et al.*, 1955; Miller *et al.*, 1958, 1960). Recent series, however, still indicate a significant incidence of bacteriuria in association with indwelling catheters and in particular in relation to prostatectomy (Mahoney and Persky, 1965; Singh, Tresidder and Blandy, 1973). The object of this study was to investigate the route by which bacteria enter the bladder in the catheterised male.

Patients and Methods

All patients from the urological ward undergoing open or transurethral prostatectomy between July 1972 and February 1973 were investigated; only those admitted to hospital with infected urine were excluded. Systemic antimicrobial drugs were not given prophylactically but some patients did receive antibiotics at the time of surgery for reasons unrelated to their urinary tract. No topical urethral antibiotic or antiseptic preparation was used. Urethral specimens were obtained by insertion of a serum-coated swab into the fossa navicularis. A mid-stream specimen of urine was collected before instrumentation and subsequent specimens were obtained by needle aspiration of the catheter tubing after swabbing with 70% alcohol. Urethral swabs and urine specimens were taken before catheterisation or operation and daily thereafter until removal of the catheter.

Bacteriological Methods

Urethral Swabs. These were cultured on blood agar (Oxoid blood agar base No. 2 CM 271 with 4% defibrinated horse blood) and on C.L.E.D. agar (Oxoid CM 301) incubated aerobically at 37°C for 24 hours. No attempt was made to culture anaerobic bacteria from the urethra.

Urine Specimens. These were cultured on C.L.E.D. agar incubated aerobically at 37°C; a standard loop which delivered approximately 0.005 ml urine was used so that an approximate bacterial count could be made. If no organisms grew on this media and more than 5 white cells per high power field were present on microscopy of the uncentrifuged specimen, further cultures were set up on blood agar with prolonged incubation to allow fastidious or slow-growing organisms to grow. Bacteriuria was defined as 10^5 or more organisms per ml of urine in any specimen but lower counts were accepted if the organism persisted.

Identification and Typing of Organisms

All organisms isolated from the urethra and urine were fully identified using the laboratory's routine range of biochemical tests and their sensitivity to a range of antimicrobial drugs was determined. Where possible organisms were typed in order to show that the same strain which had colonised the urethra had entered the urine. For certain organisms, for example, *Streptococcus faecalis* and non-swarming strains of *Proteus* typing was not possible and in these cases the strains

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were compared on the basis of biochemical tests and antimicrobial sensitivity patterns. Strains of *Staphylococcus aureus* were phage-typed; *Staphylococcus albus* was classified using the method described by Baird-Parker (1963). No attempt was made to serotype the *Escherichia coli* isolates since although the organism appeared on the urethra it never subsequently entered the bladder. *Klebsiella* species were typed using commercial antisera (Difco) to known capsular strains by the method described by Casewell (1972). Strains of *Proteus mirabilis* were compared using Dienes' phenomenon. The indole-positive *Proteus* spp were not typed. *Pseudomonas aeruginosa* was pyocine typed (Gillies and Govan, 1966).

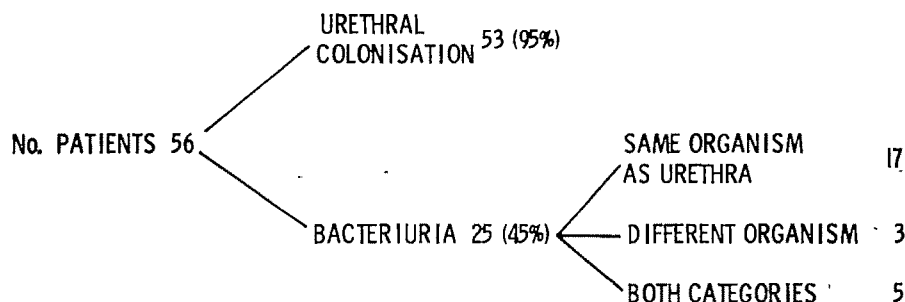


Fig. 1

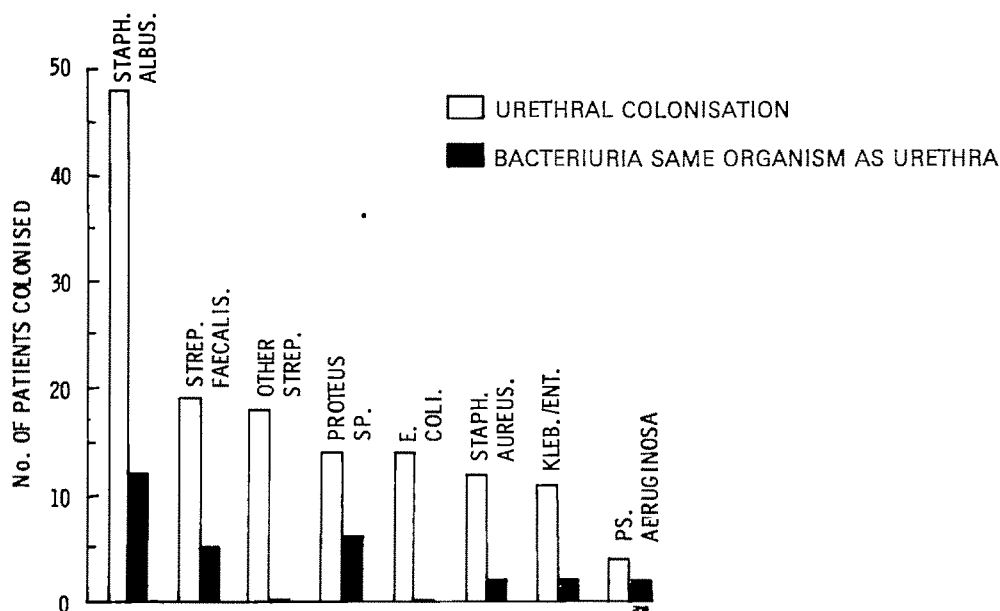


Fig. 2

Results (see Fig. 1).

56 patients were investigated and bacterial colonisation of the urethra, often with more than one organism, was found in 53 (95%). All but 10 of these 53 patients were already carrying bacteria on the urethra before instrumentation. The organisms present initially did not necessarily persist and other bacteria were subsequently acquired. Figure 2 shows the organisms colonising the urethra. *Corynebacterium* sp have been excluded, they were only ever present in very small num-

bers and in our experience do not cause urinary infection in the catheterised male. Urethral colonisation most frequently occurred with *Staph. albus* and here the culture was sometimes heterogeneous with sometimes as many as 3 different strains growing. Streptococci were also common, about half of them being *Strep. faecalis*; *Proteus* spp, *E. coli*, *Klebsiella* spp, *Enterobacter cloacae* and *Pseudomonas aeruginosa* were all grown.

In 25 of the 56 patients, bacteriuria developed and in 17 of these the organisms infecting the bladder were the same as those previously cultured from the urethra. In 3 patients the infecting organism had not previously been identified on the urethra; however the method used for sampling the urethral flora was of necessity rather crude and quite possibly not all the organisms colonising the urethra were recovered on every occasion. A further 5 patients acquired infection from the urethra but were also infected with a second organism not previously identified on the urethra. The bacteria which entered the bladder having previously colonised the urethra are shown in Figure 2. It is of interest that 50% of the *Proteus* strains colonising the urethra entered the urine, and about 30% of the *Strep. faecalis*; whereas of the 14 *E. coli* grown from the urethra, not one entered the bladder. Obviously the numbers involved here are small and it is impossible to speculate further about the ease with which any one potential urinary pathogen will enter the bladder.

There were 3 episodes of *E. coli* bacteriuria in this study and all appeared in the urine without initial colonisation of the urethra; it is worth recording that in 2 of the 3, there was definite evidence of interruption of the closed drainage system and in the 3rd, prostatic calculi removed at operation were found to harbour the same *E. coli*.

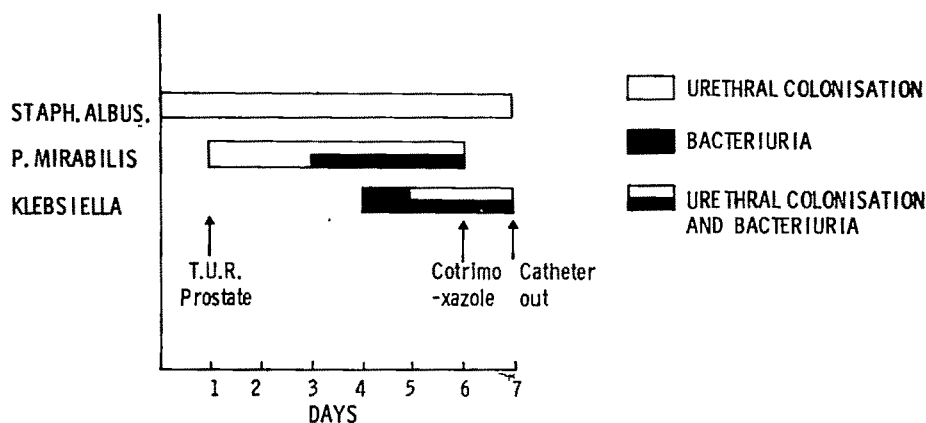


Fig. 3

Case Report

Figure 3 illustrates the urethral colonisation and its relation to bacteriuria in 1 of the patients studied who was undergoing a transurethral resection of prostate. *Staph. albus* persisted on the urethra from before surgery or catheterisation throughout the period of study but never entered the urine. *P. mirabilis* appeared on the urethra on the morning following surgery and entered the urine within 2 days. On the 4th postoperative day a *Klebsiella* was grown from the urine which had not been previously identified on the urethra though it did subsequently appear there.

Time Interval

The time interval between bacterial colonisation of the urethra and the development of bacteriuria is shown in Figure 4. In the majority of cases the organism reached the bladder in from 1 to 3 days.

Effect of Antibiotics

Systemic antibiotics were given to 15 of the 56 patients studied, though not as a routine prophylactic measure. The effect of antibiotics both on urethral colonisation and on the subsequent development of bacteriuria is shown in Figure 5. The figures are too small to be significant but there is a suggestion that although systemic antibiotics would seem to have little effect on urethral colonisation they may prevent organisms on the urethra from entering the bladder.

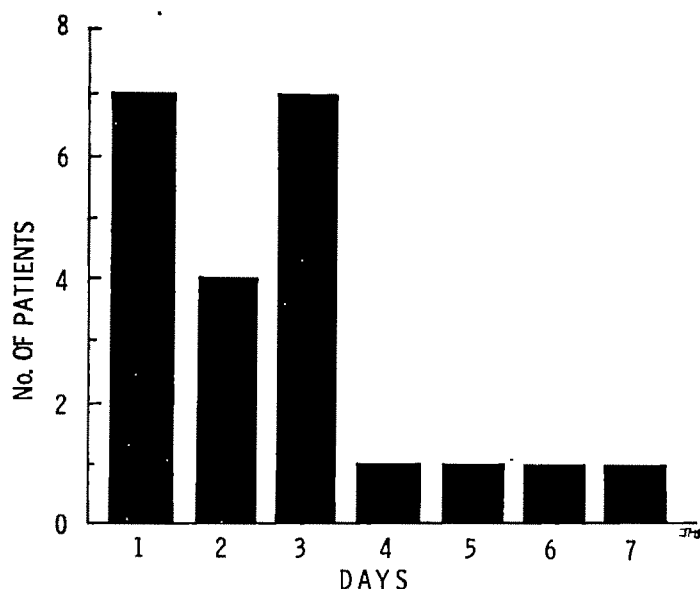


Fig. 4

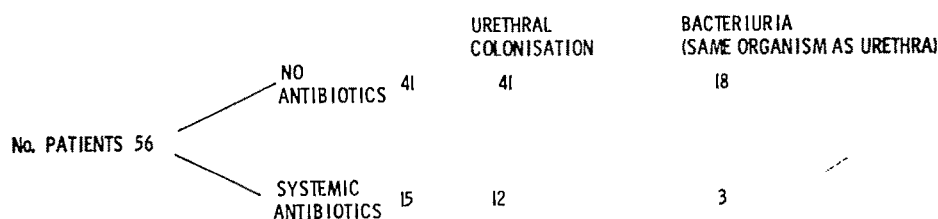


Fig. 5

Discussion

The concept of ascending urethral infection in relation to indwelling catheters is of course not new; but surprisingly few bacteriological studies have been undertaken to show the importance of this route in causing infection.

In 1954, Shackman and Messent, in a study of the effect of an indwelling catheter on the bacteriology of the male urethra and bladder, concluded that there was little relationship between the bacterial flora of the 2 sites. Their overall pattern of infecting organisms was somewhat different from ours and although they do not comment on the type of catheter-drainage used in their patients, at that time it was almost certainly open drainage. Three years later, Kass and Schneiderman (1957) showed that colonies of *Serratia marcescens* applied to the urethra could be recovered

from the bladder in 1 to 3 days in the 3 semicomatose catheterised patients they studied. In a series of papers from the Bristol group, the importance of closed catheter drainage was emphasised, and the threat from urethral organisms was recognised, though could not be demonstrated (Miller *et al.*, 1958, 1960). They recommended the use of an antiseptic gel for urethral instillation before catheterisation. More recently in America, Brehmer and Madsen (1972) demonstrated, in a similar study to this, that the main route by which the bladder becomes infected in the catheterised male is from the fossa navicularis along the catheter into the bladder. However, they cultured specimens less frequently than was done in this series, and no bacteriological details are given in their paper thus precluding a detailed comparison with our study.

It would seem not unreasonable to conclude that when bacteriuria occurs in the catheterised male, the infecting organism has almost always first colonised the urethra. Brehmer and Madsen (1972) found that this retrograde transurethral route of bladder infection could be effectively interrupted by daily antiseptic sitz baths and application of a topical antibiotic spray to the perineum. We found that although urethral colonisation occurred just as frequently whether systemic antibiotics were given or not there was a suggestion that antibiotics might prevent the urethral flora from establishing an infection in the bladder. It may well be that a combination of topical and systemic antimicrobial therapy may provide the best defence against infection by this route.

Summary

In a study of 56 patients undergoing prostatectomy, it has been shown that when bacteriuria developed in the presence of an indwelling catheter, the infecting organism could almost always be found colonising the urethra from 1 to 3 days before it entered the bladder.

We thank Mr K. E. D. Shuttleworth and Mr R. W. Lloyd-Davies for permission to study their patients and Miss C. Jenkins F.I.M.L.T. for technical assistance. We are also grateful to Dr M. Casewell and Miss A. King for assistance with typing of organisms.

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Discussion

J. P. MITCHELL (*Bristol*)

Mr Mitchell reminded the speaker that the assessment of urethral flora was virtually impossible, and that his swabs should be regarded more correctly as meatal flora. Any instrument used to swab the urethra proximal to the external urinary meatus would inevitably carry organisms up the urethra on the tip of the instrument itself. Hence all urethral swabs were little more than meatal cultures and, for this reason, the Bristol team felt unjustified in attempting further experiments in order to break down their figures, which showed marked reduction in the postoperative infection rate from 3 factors collectively. Namely:

- (1) careful maintenance of closed drainage.
- (2) meatal toilet and
- (3) urethral disinfection.

Mr Mitchell agreed that the gels containing chlorhexidine varied in their antiseptic efficiency, and this was due to possible deterioration with storage for periods of longer than a month and, secondly, the type of vehicle used, as it had been found that tragacanth gel inactivated chlorhexidine very quickly while methyl oxycellulose gel was satisfactory for at least 1 month.

Investigation and Treatment of the Subfertile Male

W. F. HENDRY, I. F. SOMMERVILLE, R. R. HALL and R. C. B. PUGH

Institute of Urology and St Peter's Hospitals, London, WC2 and Chelsea Hospital for Women, London, SW3

In approximately 10% of marriages there is difficulty in producing a pregnancy, and the husband may be partly or completely responsible for the subfertility in 40% of couples (Buxton and Southam, 1958). In most hospitals, subfertility in women is exhaustively investigated and intensively treated by our gynaecological colleagues. All too often, however, the husbands are merely asked to produce a specimen for seminal analysis, and their fertility is then judged, often *in absentia*. Oligozoospermia is usually taken to indicate that the husband is to blame for the barren marriage, and its treatment is frequently dismissed as unrewarding, or as a waste of time. As urologists, we should be prepared to spend as much time and effort treating the husbands as the gynaecologists spend treating the wives.

Patients and Investigations

Between January 1971 and December 1972, 166 subfertile men have been investigated and treated at the Male Fertility Clinic at the Chelsea Hospital for Women, which is run in association with the Institute of Urology and St Peter's Hospitals.

Clinical evaluation included detailed marital, sexual, present and past medical, and social history. Patients were then examined lying and standing, and the type of underpants was noted.

Seminal analysis was judged on at least 2 specimens produced after 2-4 days abstinence. Oligozoospermia was accepted as counts of less than 20 million sperms per ml (Macleod, 1951). Counts of more than 20 million per ml with motility of less than 30% moving actively within 3 hours of production of the specimen were defined as asthenospermia.

Plasma testosterone was measured by radio-immunoassay (Collins *et al.*, 1972), on blood samples taken between 9.00 am and 12 noon. Urinary gonadotrophins were assayed in 2 24-hour urine collections: luteinising hormone has been measured throughout this study, but follicle stimulating hormone assay has only recently been introduced, and insufficient results are available for inclusion in this analysis.

Chromosome analysis on buccal smears and peripheral blood has been performed by Professor P. E. Polani at the Paediatric Research Unit at Guy's Hospital. Meiotic studies on testicular biopsy material have also been made, and will be reported elsewhere.

Testicular biopsies were taken under general anaesthesia on all patients with proven oligozoospermia or azoospermia. Biopsies were immediately fixed in Bouin's solution, and stained with haematoxylin and eosin. Spermatogenesis was assessed by one observer (RCBP) according to the method described by Johnsen (1970). This provides a testicular biopsy score count, which is expressed as a figure between 1 (no cells in tubular section) and 10 (normal complete spermatogenesis).

Antibody studies have been introduced since the report by Halim *et al.* (1973), but too few results are available yet to permit analysis in this report.

Read at the 29th Annual Meeting of the British Association of Urological Surgeons in London, June 1973.

Treatment and Results

All 166 patients were given general advice on the optimum timing of intercourse, and excessive smoking or alcohol intake was discouraged. In addition loose underpants were strongly recommended at the initial visit, and occasional checks were made thereafter to ensure that this advice was followed. The patients were then treated in 5 main groups, according to the findings on examination and the results of seminal analysis.

Group I: General Measures Only

In 25 cases, correction of timing of intercourse together with loose underpants produced either a normal seminal analysis (13 patients) or pregnancy in the spouse (12 patients) without any need for further treatment (Table I).

Table I

Group I (25 patients). Results Obtained by General Measures Only (loose pants and correct timing)

	Number	Sperm Count (millions/ml)				
		Azoospermic	1-10	11-20	21-40	41+
Before	25	...	...	11	14	..
After treatment	...	...	...	...	2	11
+ 12 pregnancies (48%)						

Group II: Ligation of Varicocele

Left sided varicocele was found in 32 cases (19%). These patients underwent exploration of the spermatic cord in the inguinal canal. By raising the head of the operating table by about 10°, the venous abnormality could be readily defined and corrected. In 21 cases only the internal spermatic vein was ligated, at the level of the internal inguinal ring; in 9 cases both internal spermatic and cremasteric veins were ligated. In 2 cases only the cremasteric veins were ligated, and in both of these cases subsequent re-exploration was required for persistent varicocele and low sperm count, which was corrected after ligation of the internal spermatic vein at the second operation.

Table II

Group II (32 patients). Results Obtained by Ligation of Varicocele

	Number	Sperm Count (millions/ml)				
		Azoospermic	1-10	11-20	21-40	41+
Before	32	5	7	11	6	3
After 3 months	29	4	4	5	10	6
After 6 months	17	...	2	1	5	9
More than 6 months	8	...	2	...	3	3
Pregnancies		...	1	2	1	1

The results of this operation are shown in Table II. 22 patients (69%) showed distinct improvement in seminal analysis, as judged by an increase in sperm count to more than 20 million per

ml in oligozoospermic patients, or return of normal motility in asthenospermic patients. Five pregnancies (16%) have been obtained so far in this Group.

Group III: Mesterolone Therapy

In 69 patients the general measures outlined above were supplemented by mesterolone 100 mg daily for 1 year. The results in 58 patients with average initial sperm counts of less than 20 million per ml are shown in Table III, where improvement is taken as a rise in average sperm count to more than 20 million per ml. About half of the patients with average initial counts

Table III

Group III. Mesterolone 100 mg Daily for 1 Year. Results Obtained with 58 Patients with Initial Counts of Less than 20 million per ml, Expressed as Percentage Showing Improvement to More than 20 million per ml.

		Initial Sperm Count (millions/ml)		
		Azoospermic	1-10	11-20
	Number	7	24	27
3 months	58	0	29%	63%
6 months	45	0	33%	78%
9 months	31	...	57%	70%
1 year	14	...	50%	75%

Table IV

Group III. Mesterolone 100 mg Daily for 1 Year. Results Obtained with 69 Patients with Initial Counts of Less than 40 million per ml, Expressed as Percentage Showing Improvement to More than 40 million per ml.

		Initial Sperm Count (millions/ml)			
		Azoospermic	1-10	11-20	21-40
	Number	7	24	27	11
3 months	69	0	17%	22%	27%
6 months	63	0	5%	35%	38%
9 months	37	...	29%	47%	50%
1 year	16	...	16%	50%	2/2
Pregnancies		...	7	4	2

of 1-10 million per ml, and three-quarters of those with initial counts of 11-20 million per ml showed improvement. Early in the series, 7 patients with azoospermia were treated with mesterolone, without improvement. Subsequently, these patients were excluded from this group.

The results in 69 patients with average initial counts of less than 40 million per ml are shown in Table IV, where improvement is taken as a rise in average count to more than 40 million per ml. Less than half of the patients showed improvement to this level.

One patient developed a seminoma of the testis during therapy; however, close enquiry has failed to reveal any other instances of this disease in other centres using this drug, and it seems reasonable to ascribe this isolated case to coincidence.

13 pregnancies (19%) were obtained in this Group (see Table IV).

Group IV: Fluoxymesterone Therapy

20 patients had normal sperm counts with persistently poor motility, despite the general measures outlined above. These patients were treated with fluoxymesterone 5 mg daily for 3-6 months. In 13 cases (65%) there was distinct improvement in motility (to more than 30% moving actively within 3 hours), and 3 pregnancies occurred (15%).

Group V: Azoospermia

20 patients showed azoospermia. In 10 cases there was testicular atrophy, and no further treatment was recommended. In 8 cases with normal sized testes, epididymo-vasostomy was performed: 1 patient subsequently had a few dead spermatozoa in the ejaculate (operation performed by Mr D. M. Wallace) but azoospermia persisted in the other 7 cases. One patient with absent vasa underwent epididymo-seminal vesiculostomy with saphenous vein graft interposition (operation performed with Mr D. M. Wallace) without improvement. One patient who had previously been treated for tuberculosis had no ejaculate, and X-ray showed extensive calcification of vasa and seminal vesicles.

Endocrine Results

The results of plasma testosterone assays in the various treatment groups are shown in Table V, where they may be compared with results obtained with 120 healthy sailors (samples kindly provided by Surg. Cdr. N. J. Blacklock, R.N.). In Group III, patients who responded to mestosterone had slightly but not significantly, lower mean plasma testosterone levels compared to those who showed no response. In Group IV, patients with asthenospermia who showed improvement with fluoxymesterone had significantly lower plasma testosterone levels than patients who failed to show improvement (by *t* testing, $P < 0.001$).

Table V

Mean ($\pm$ S.D.) Plasma Testosterone (ng/100ml)
Results in Healthy Men, and in the Various Treatment Groups

Group	Number	Mean ($\pm$ S.D.) Plasma Testosterone (ng/100 ml)
Healthy men	120	566 $\pm$ 236
I	21	431 $\pm$ 179
II	24	452 $\pm$ 190
III—Improved	27	450 $\pm$ 167
Not improved	27	536 $\pm$ 210
IV—Improved	9	330 $\pm$ 65
Not improved	6	615 $\pm$ 129
V—Ep-vasos.	5	384 $\pm$ 136
Atrophy	8	343 $\pm$ 113

Urinary luteinising hormone levels in the various treatment groups are shown in Table VI. There were no significant differences between the groups, although slightly elevated levels were noted in azoospermic patients with testicular atrophy.

Chromosome Studies

Two patients were found to have Klinefelter's syndrome, 1 patient had 46 XY/47 XXY mosaicism, and 4 patients had 46 XYq+ chromosomes.

Testicular Biopsies

The mean testicular biopsy scores for patients with varicoceles (Group II) are shown in Table VII. The mean score for patients who showed improvement after operation (8.50 ± 1.12) was

Table VI

Mean ($\pm$ S.D.) Urinary Luteinising Hormone Levels (I.U. per 24 hours) in the Various Treatment Groups

Group	Number	Mean ($\pm$ S.D.) Urinary Luteinising Hormone (I.U./24 hours)
I	11	29.2 ± 19.0
II—Improved	12	27.7 ± 10.4
Not improved	9	36.6 ± 28.9
III—Improved	15	25.5 ± 7.2
Not improved	26	30.5 ± 15.9
IV—Improved	9	37.0 ± 10.1
Not improved	6	34.2 ± 15.7
V—Ep-vasos.	4	23.0 ± 13.3
Atrophy	7	43.1 ± 16.6

Table VII

Mean ($\pm$ S.D.) Testicular Biopsy Score Counts (after Johnsen, 1970) in Group II (varicocele) Patients

	Number	Mean ($\pm$ S.D.) Testicular Score count
Improved	17	8.50 ± 1.12
Not improved	9	6.40 ± 3.29
Left testis	10	6.94 ± 2.94
Right testis	10	6.88 ± 2.86
Pregnancy	4	8.25 ± 1.16
		(Range 6.16 to 9.70)

Table VIII

Mean ($\pm$ S.D.) Testicular Biopsy Score Counts (after Johnsen, 1970) in Group III (mesterolone) Patients

	Number	Mean ($\pm$ S.D.) Testicular Score Count
Improved	21	8.77 ± 1.37
Not improved	25	6.82 ± 2.92
Pregnancy	8	8.73 ± 1.15
		(Range 6.07 to 9.69)

significantly higher than for patients who did not (6.40 ± 3.29) (by *t* testing, $P < 0.01$). In 10 patients with varicoceles who had bilateral testicular biopsies, there was no difference between the two sides. The mean score for 4 patients who produced pregnancies was 8.25 ± 1.16 , with a range from 6.16 to 9.70.

The results in patients treated with mesterolone (Group III) are shown in Table VIII. Patients who showed a good response to therapy had a significantly higher mean score (8.77 ± 1.37) than patients who did not show improvement (6.82 ± 2.92) (by *t* testing, $P < 0.01$). The mean score for 8 patients who produced pregnancies was 8.73 ± 1.15 , with a range from 6.07 to 9.69.

Six patients in Group V (azoospermia) who underwent epididymo-vasostomy had a mean score of 8.93 ± 1.4 , as compared to 10 patients with testicular atrophy (2.07 ± 0.5).

Discussion

These results confirm that fertility can be improved in many of these patients, and that a considerable number of pregnancies may be obtained. The results in Group I demonstrate the importance of simple general measures, including firm reassurance combined with correction of obvious faults in timing. Modern fashions have persuaded most young men to wear tight-fitting pants and trousers, and considerable efforts may be required to persuade these men to change into looser garments. There seems little doubt that this is worthwhile since Robinson and Rock (1967) have demonstrated an 86% decline in sperm count as a result of wearing tight-fitting insulated underpants, with rapid return to greater than pre-treatment levels once they were discarded.

Varicocele may be found in about 10% of the normal population (Johnson, Pohl and Rivera-Correa, 1970), and in about 20% of men attending a subfertility clinic (Davis *et al.*, 1965), provided that the patient is examined standing up in good light. A careful search is certainly worthwhile, since there is good evidence that improvement in seminal analysis is equally good after ligation of small or large varicoceles (Kiszka and Cowart 1960; Dubin and Amelar, 1970). The aetiology and operative approach to correction of varicocele has been the subject of debate for many years. However, since Ahlberg *et al.* (1966) demonstrated the presence of internal spermatic vein reflux by retrograde venography in all 18 men with varicoceles, and in 4 patients with persistent varicocele after operation, but in none of 9 controls or 6 patients cured by operation, there seems little doubt that the primary defect is deficiency of the valves in the internal spermatic vein. The operative experience described in this series suggests that the resulting venous abnormality may conveniently be considered in 2 stages (figure): in stage I only the internal spermatic vein is dilated, and needs to be ligated; in more advanced, stage II cases, however, secondary dilatation and incompetence of the cremasteric system may develop, and both systems may then require ligation. This is most easily achieved by the inguinal approach, as recommended by Ivanissevich (1960). The supra-inguinal approach (Palomo, 1949) suffers from the disadvantage that the secondary cremasteric incompetence may be missed, and the scrotal approach may be associated with a high incidence of testicular atrophy (Fritjofsson *et al.*, 1966.) There is ample evidence that improvement in seminal analysis may be expected in 60-70% of cases, and pregnancies may result in up to 40% of cases (Tulloch, 1955; Charny, 1962; Scott & Young, 1962; Hanley and Harrison, 1962; Brown, Dubin and Hotchkiss, 1967; Macleod, 1969) with a peak incidence 6 months after operation (Dubin and Amelar, 1970).

Mesterolone is a weak oral androgen, which has given mixed results in the treatment of oligozoospermia. Niermann and Nolting (1966), Todeschini *et al.* (1970) and Sturde (1971) have described improvement in sperm count in about half the patients treated, but Swyer (1972) noted improvement in only 5 of 17 men. The precise mode of action is unknown, but it has been suggested that it may improve the androgen environment of the genitalia, without suppressing pituitary gonadotrophins. Sturde (1971) noted an increase in seminal fructose and prostaglandin levels during treatment, which is similar to the effects produced by testosterone (Gunaga *et al.*, 1971). In the present series, mesterolone was combined with general measures, and it is not possible to be sure how much each of these factors contributed to the observed improvement in spermatogenesis.

Analysis of plasma testosterone levels in patients treated with mesterolone (Group III) or fluoxymesterone—a stronger oral androgen—(Group IV) showed that patients who responded to

treatment had lower average pre-treatment levels of testosterone than patients who failed to respond, although this difference was significant only in Group IV patients. It is possible that this estimation may be helpful in selecting patients most suitable for androgen therapy. Mauss (1972) has described elevated levels of urinary L.H. in androgen-responsive oligospermic men, but no such differences were found in this study. Franchimont *et al.* (1972) found no correlation

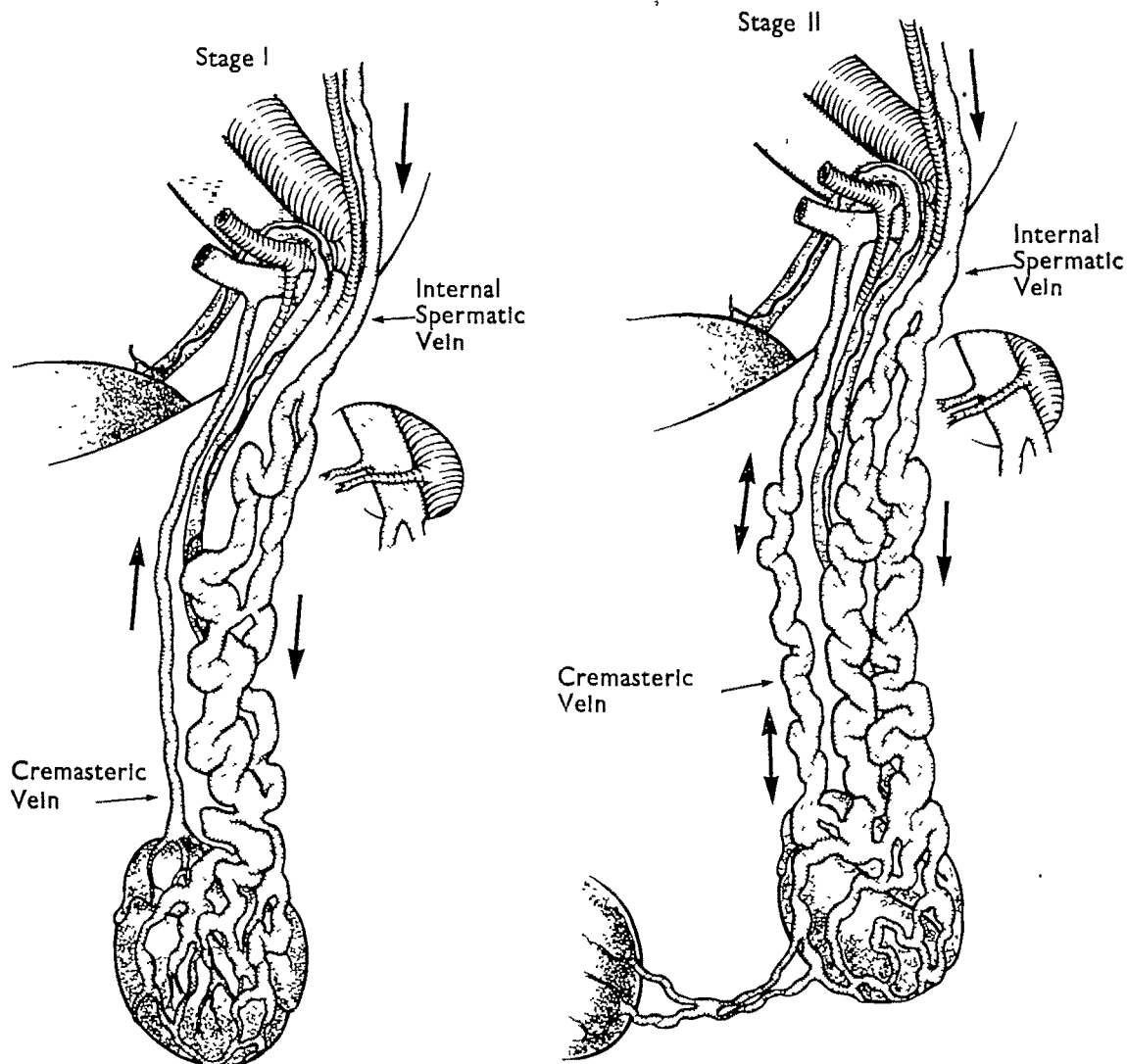


Figure. Stages in development of varicocele: in Stage I the primary defect lies in the internal spermatic vein, and ligation should be curative; in Stage II there develops secondary varicosity in the cremasteric system, which may become incompetent as well—both systems should be ligated.

between serum L.H. and sperm count or stage of spermatogenesis on testicular biopsy, although F.S.H. was increased in cases of azoospermia with gametogenesis arrested prior to spermatid differentiation. Gonadotrophins and clomiphene have not been used in this study, but clearly these estimations may be helpful in selecting cases suitable for this form of treatment.

The testicular biopsy score account system devised by Johnsen (1970) provides an accurate method of registering the degree of spermatogenesis, and gives a mathematical index of the

functional state of the testicular tissue. Analysis of the results obtained in this series suggests that this may be useful in predicting which cases may be expected to respond to treatment, and indicate that pregnancy is unlikely with a score count of less than 6.0, which represents the point at which spermatids appear in the tubules in the biopsy material. The similarity of changes in left and right testes in patients with left sided varicocele confirms the findings of Dubin and Hotchkiss (1969). In most cases in this series only the larger testis was biopsied, since there is evidence that bilateral testicular biopsies may produce temporary suppression of spermatogenesis (Rowley, O'Keefe and Heller, 1969). The biopsy material examined in this series has also been graded according to mean tubular diameter, percentage of tubules at each step, and for Leydig cells, and a clinico-pathological correlation of this data will be recorded in detail elsewhere.

Summary

166 men have been treated for subfertility. All patients were given general advice, loose underpants were recommended, and obvious timing errors were corrected.

In 25 cases (Group I) no further measures were required, and the sperm count returned to normal, or pregnancy ensued (12 cases).

Varicocele was found and ligated in 32 cases (Group II); seminal analysis improved in 22 patients (69%) and 5 pregnancies occurred.

69 patients (Group III) with oligozoospermia were treated with mesterolone 100 mg daily for 1 year: seminal analysis improved in 50-75% of cases, and 13 pregnancies were produced.

20 patients (Group IV) with asthenospermia were treated with fluoxymesterone 5 mg daily for 3-6 months: motility improved in 65% of cases, and 3 pregnancies resulted.

20 patients (Group V) had azoospermia: 10 had testicular atrophy, and received no treatment; 8 patients underwent epididymo-vasostomy, and some dead sperms appeared in the ejaculate in 1 case.

Analysis of plasma testosterone results shows that androgen responsive patients have lower average levels of testosterone as compared to patients who failed to respond. Urinary L.H. levels showed no significant differences between the various groups.

Testicular biopsy score counts showed that patients who responded to treatment had significantly better spermatogenesis than those who did not respond; pregnancies occurred provided that there was evidence of spermatid differentiation. This method of assessing testicular biopsy material appears to provide a useful prognostic index.

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The Spread of Tuberculosis in the Male Genital Tract: An Experimental Study in Guinea Pigs

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The prostate and/or the seminal vesicles are generally regarded as the primary foci of genital tuberculosis in men. Tubercle bacilli reach these organs by way of the blood stream or the urine, and infection may spread to the scrotal organs by way of the ductus deferens. Other routes of spread have not been clearly documented. In order to investigate whether genital tuberculosis can spread via the lymphatics as well as by the canalicular route, the spread of genital tuberculous infection has been studied experimentally in guinea pigs. In 1 group of animals the spread of infection from the urinary bladder to the genitalia was investigated, in another group, the spread of infection within the genital tract.

58 guinea pigs were inoculated with 0.05 ml of a standardised dilution of a human strain of tubercle bacilli (H₃₇Rv) into the urinary bladder wall, epididymis or seminal vesicle. To prevent leakage and spread a strongly bactericidal plastic film was applied over the site of injection before the needle was withdrawn.

The animals were divided into 6 groups which were treated as follows:

- A 1 Inoculation into the urinary bladder wall.
- A 2 Inoculation into the urinary bladder wall after resection of the ductus deferens.
- B 1 Inoculation into the epididymis.
- B 2 Inoculation into the epididymis after resection of the ductus deferens.
- B 3 Inoculation into the seminal vesicle.
- B 4 Inoculation into the seminal vesicle after resection of the ductus deferens.

The animals were killed after 3-8 weeks and the extent of the tuberculous infection was determined macroscopically, histologically and bacteriologically. The diagnosis results obtained by the use of haematoxylin-eosin staining, staining according to Ziehl-Neelsen and fluorescent staining were compared with each other and with the results of culture on Löwenstein-Jensen medium. Fluorescent staining with Auramine-rhodamine was found to be clearly superior to the classical Ziehl-Neelsen method and about as effective as culture for the demonstration of organisms. The bacteria were more clearly visible if epi-illumination was used instead of transillumination, especially at higher degrees of magnification. The conventional histological method, using haematoxylin-eosin, in combination with fluorescence microscopy provided an adequate means of mapping the spread of tuberculous infections in the animals.

In groups A (Table I) there was spread to the prostate in nearly all animals; this spread was usually continuous, but there was evidence of lymphatic spread in some animals. Tuberculous changes were observed in the epididymis unilaterally or bilaterally in 3 of 9 animals in group A 1 and in 8 of 9 animals in group A 2. Spread to the epididymis usually occurred by way of the lymphatics.

In groups B 1 and B 2 (Table II) there was spread to the prostate and/or seminal vesicle in only 2 of 10 animals. There was spread to the homolateral epididymis in 6 of 10 animals in group B 1 and in 4 of 10 animals in group B 2. Spread to the contralateral epididymis was observed in 2 of 10 animals in group B 1 and in 1 of 10 animals in group B 2. Spread to the seminal vesicle was observed in 2 of 10 animals in group B 3 and in 1 of 10 animals in group B 4. Spread to the contralateral seminal vesicle was observed in 1 of 10 animals in group B 3 and in 1 of 10 animals in group B 4.

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B 3 and in all 10 animals in group B 4. In all groups there were tuberculous changes in the lymphatics.

From the animal experiments we have drawn the following conclusions:

1. Tuberculosis spreads from the urinary bladder to the genitalia and within them regardless of whether the ductus deferens is intact.
2. The lymphatics constitute an important route of spread both from the bladder to the genitalia and within the genital system.
3. Spread is most common from the pelvic to the scrotal genitalia.

Table I

A. Tuberculous Changes in the Genital Tract of Male Guinea Pigs Following Inoculation into the Urinary Bladder Wall

	No. of Animals	LE	LSV	P	B1	RSV	RE
1 Intact ductus deferens	9	1	1	8	9	0	3
2 Resection of d. deferens	9	4	0	5	9	0	7

□ = indicates the site of inoculation

LE = left epididymis

LSV = left seminal vesicle

P = prostate

RE = right epididymis

RSV = right seminal vesicle

B1 = urinary bladder

Table II

B. Tuberculous Changes in the Genital Tract of Male Guinea Pigs Following Inoculation into the Epididymis or the Seminal Vesicle

	No. of Animals	LE	LSV	P	RSV	RE
1 Intact ductus deferens	10 (1+)	9	0	2	0	1
2 Resection of d. deferens	10	10	1	2	0	1
3 Intact ductus deferens	10	6	10	10	0	1
4 Resection of d. deferens	10	10	10	10	1	1

Symbols see Table I.

It is, of course, impossible to apply conclusions from animal experiments directly to man. Here it is a question of a primary tuberculous infection with a relatively large number of bacteria in a previously non-immunised guinea pig. In man, genital tuberculosis is a late manifestation of the disease, and almost always occurs in previously immunised territory. It is very difficult to construct a model which would enable us to follow the spread of infection without disturbance from the preliminary immunisation. However, in general, it may be said that secondary tuberculous infection in an immunised animal takes the same overall course and spreads by the same routes as in a non-immunised host.

In recent years a rather large number of clinical cases of tuberculosis in the spermatic cord have been reported. Some of these cases including that of a patient with secondary funicular

tuberculosis which we described, support the impression that lymphatic spread occurs even in man.

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Transplantation of Interstitial Cells of the Testis

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Attempts to transplant the testis have been made since John Hunter's time, but numerous factors have prevented success. These included ignorance of aseptic techniques initially, difficulties with vascular anastomoses when whole organ transplantation was employed (Attaran and Hodges, 1966; Puchetti, 1966) and problems with immunological rejection mechanisms. However, work carried out using individual components of the testis has produced more encouraging results. Turner (1938) reported transplantation of seminiferous tubules and interstitial cells of the testis in intra-ocular sites in the rat and Williams (1950) transplanted similar tissues in millipore-type chambers in the ear of the rabbit, and showed some proliferation of the component cells.

The present experiments were devised to study the fate of free testicular grafts and their effects on primary and secondary sexual development. Homogenate suspensions of the testis containing liberated interstitial cells were grafted into various sites in castrated animals. The effects were observed in autologous and allogeneic combinations in inbred strain mice, and the survival of the cells was assessed histologically.

Materials and Methods

Transplantation was performed between (CBA-T6T6 × C57BL) F₁ hybrid mice, and between the F₁ hybrids as donors and C57BL strain animals as recipients, at the ages of 3 weeks in one group of experiments and 3 months in another group.

Bilateral orchidectomy was carried out under ether anaesthesia through a midline vertical lower abdominal transperitoneal incision. The testes were placed in a sterile petri dish with 3–4 drops of normal saline and cut up finely with scissors. A thick suspension was made of the contents of both testes and aspirated into a brain-type cannula by slowly withdrawing the plunger. The homogenate was subsequently injected into localised areas in ear pinnae and under the skin of the back and snout. The animals were weighed weekly over a period of 3 months and groups were killed at varying intervals to determine the weight, appearance and histological structure of the genital apparatus, particularly the seminal vesicles and penis. The graft areas were examined for vascularisation, sectioned, and stained with haematoxylin and eosin for histological study. Observations were also made in groups of castrated non-transplanted animals, and sham operated control mice in which the same operation was performed as above, apart from ligating the spermatic cords and removing the testes.

Results

Castrated animals gained weight more slowly than sham operated ones over the 3-month period studied (Fig. 1), the differences becoming apparent from the 1st week and statistically significant from the second. Following autologous grafting of the testes into the subcutaneous dorsal site, weight gains corresponded to those of sham operated mice from the 3rd week (Fig. 1).

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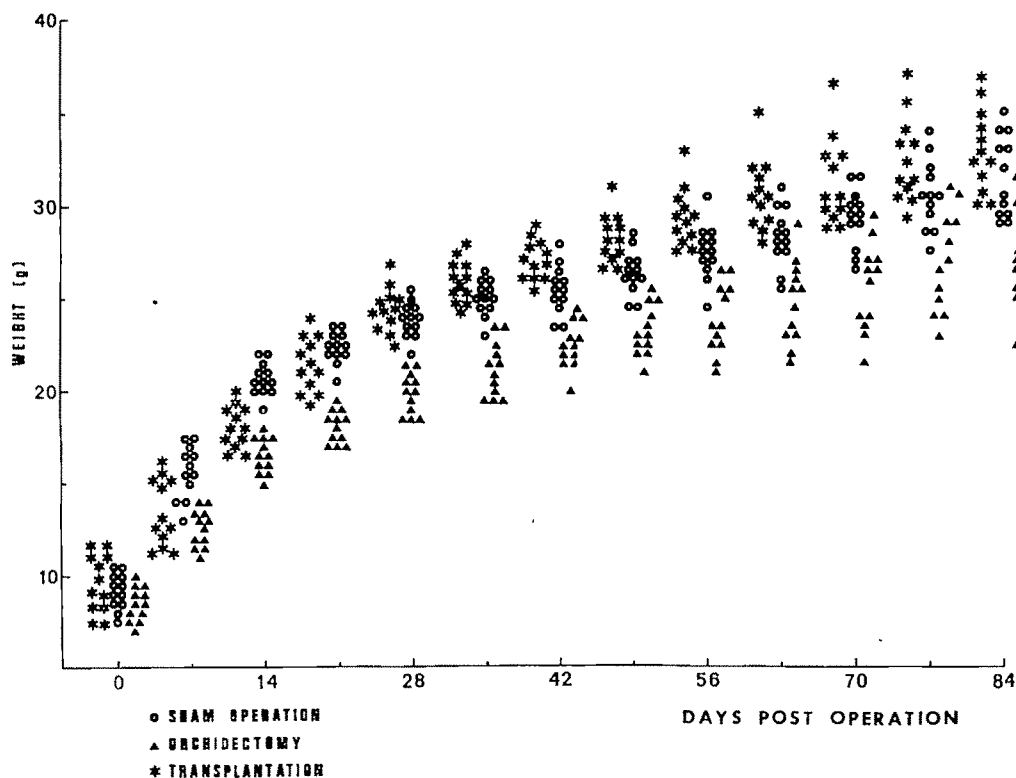


Fig. 1. Effect of orchidectomy transplantation and sham operation on body weights of 3-week-old (C57BL x CBA-T6T6)₁ hybrid mice.

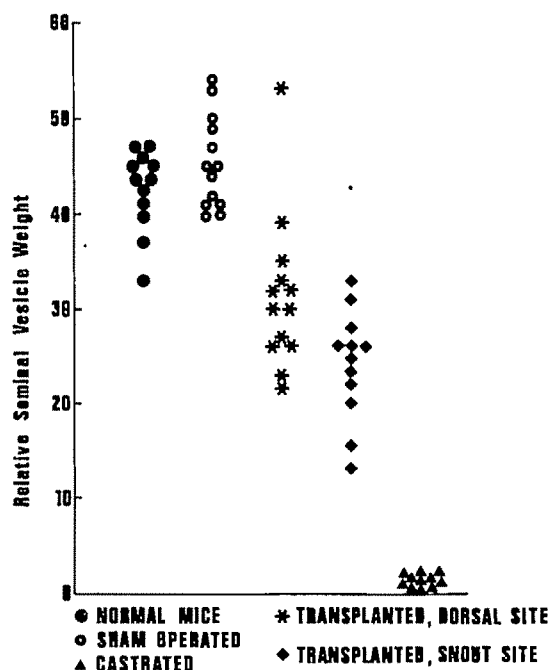


Fig. 2. Relative seminal vesicle weights of (C57BL x CBA-T6T6) F₁ hybrid mice, 3 months after operation performed on 3-week-old mice.

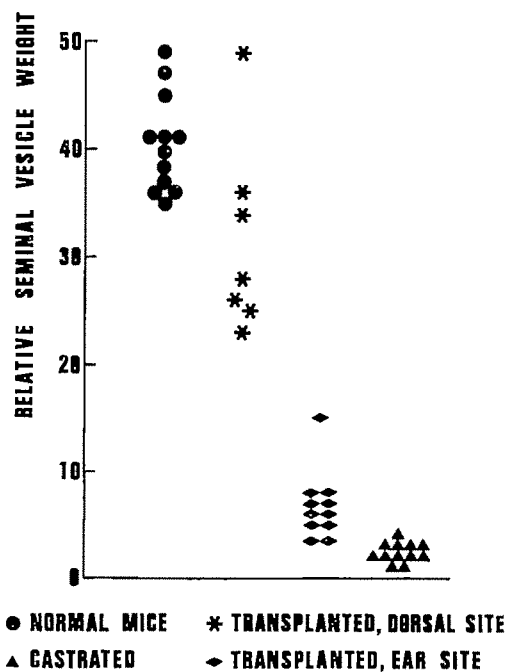


Fig. 3. Relative seminal vesicle weights of adult (C57BL x CBA-T6T6) F₁ hybrid mice, 3 months after operation.

Seminal vesicle weights are expressed as an arbitrary convenient ratio of the weight of the vesicles to the body weight of the animal:

$$\text{Relative Seminal Vesicle Weight} = \frac{\frac{1}{2} \text{ weight of both seminal vesicles (mg)}}{\text{body weight of mouse (g)}} \times 10$$

Following bilateral orchidectomy in adolescent animals, the seminal vesicles did not develop and in adults they atrophied. When testicular suspensions were implanted into the animals, development was restored, but to varying degrees according to the site employed (Figs. 2 and 3). The subcutaneous dorsal site was the most effective, relative seminal vesicle weights approximating to those of controls 3 months after grafting. Subcutaneous injection into the snout produced slightly less enlargement of the vesicles and injection into the ear pinnae least of all. However, even in the latter site, there was a statistically significant increase over the vesicle weights of

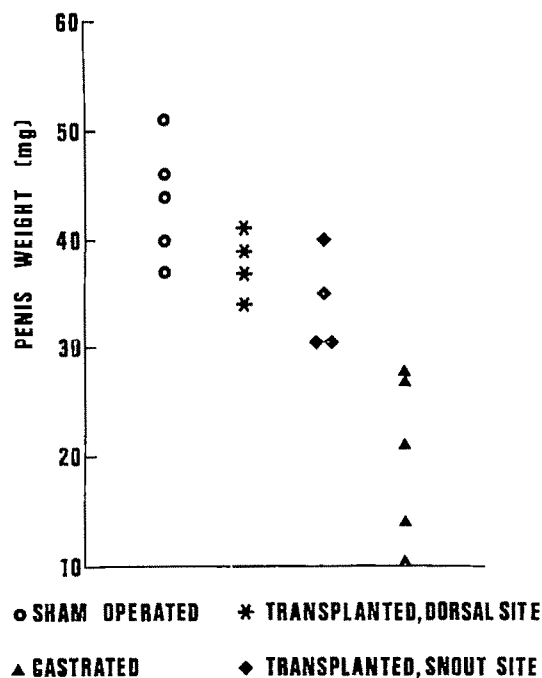


Fig. 4. Penis weights of (C57BL × CBA-T6T6) F₁ hybrid mice, 3 months after operation performed on 3-week-old mice.

castrated mice with only a few individual results overlapping. Seminal vesicles from castrated animals contained little or no secretion, whereas those from normal, sham operated and transplanted animals showed distension of the collecting spaces with secretory material. Changes in the size and weight of the penis followed those of the seminal vesicles (Fig. 4).

The graft areas, 3 months postoperatively, were seen as light pink localised swellings which had obtained a good blood supply from surrounding structures. The blood vessels were easily visible with the naked eye and were prominent in many cases (Fig. 5). On histological examination there was initially some round cell infiltration with proliferation of fibroblasts and occasional giant cell formation. Seminiferous tubules were atrophic in all cases and there was no evidence of spermatogenesis. However, interspersed between this tissue were small groups of larger cells containing granular type cytoplasm which stained pinker with haematoxylin and eosin than the surrounding structures (Fig. 6). These cells were indistinguishable from those of normal mouse interstitial cells. Mitoses were not seen but the impression was obtained that the clumps became larger with progression of time over the 3-month period studied.

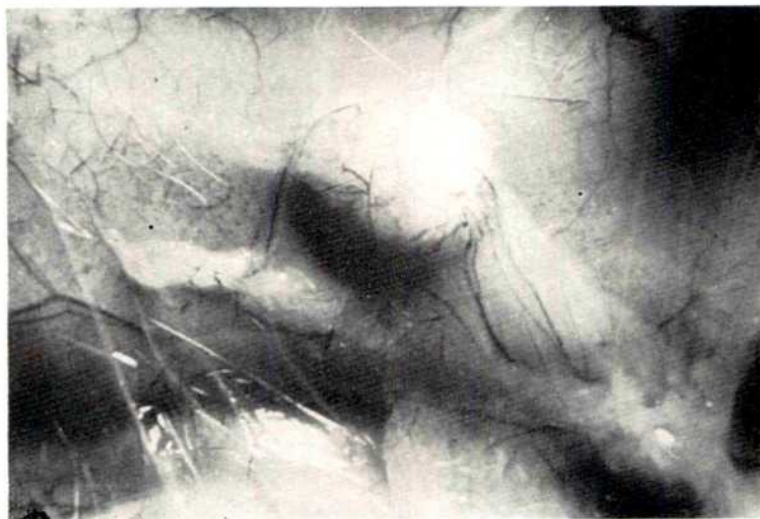


Fig. 5. Free testicular graft, subcutaneous dorsal site 3 months after transplantation, showing a good blood supply from surrounding tissues.



Fig. 6. Group of interstitial cells from a subcutaneous graft 3 months after transplantation.

In a preliminary group of experiments observations made in adult mice 7 weeks after castration followed by allotransplantation showed atrophy of seminal vesicles similar to those of control castrated animals, while in autotransplanted mice at the same period the seminal vesicles were considerably larger (Fig. 7). A yellowish swelling was present in the area of the allograft with no obvious vascularisation from the surrounding tissues and no cells resembling interstitial cells were found on histological examination.

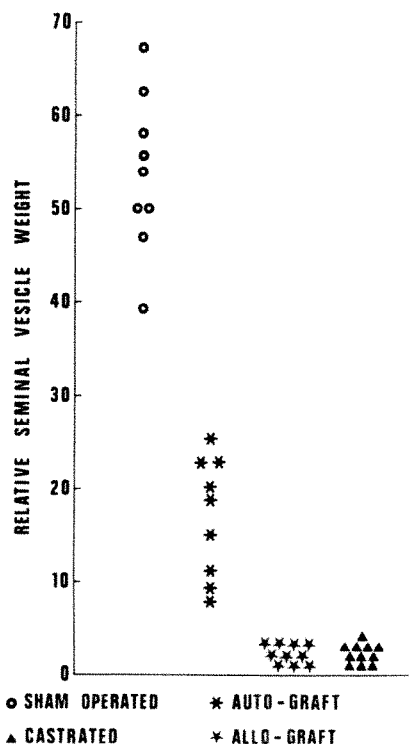


Fig. 7. Auto and allotransplanted adult C57BL mice relative seminal vesicle weights 7 weeks after operation.

Discussion

The results of the experiments have shown that following castration of young mice, total body weights increase more slowly than those of normal animals and that development of the seminal vesicles and the penis is markedly impaired. Restoration to normal values was obtained after subcutaneous autotransplantation of testicular homogenates, the grafts became vascularised and cells indistinguishable from normal interstitial cells were a constant feature on histological examination. Even though direct evidence of endocrine secretion of either androgens or gonadotrophins were not available in these experiments, no alternative explanation to the observed facts is likely other than that actively secreting interstitial cells were transplanted. Transplantation under the skin of the back of the animals produced better development of seminal vesicles than in the possibly more restricted sites under the skin of the snout or in the ear pinnae. Although cells resembling interstitial cells were seen in all the sites studied, it is likely that the cells were freer to divide and possibly received a better blood supply in the looser subcutaneous region of the back.

Spermatogenesis was not seen in any of the sections examined. Seminiferous tubules rapidly atrophied, their component cells died and were phagocytosed. This pattern does not occur when

transplantation of the whole organ with vascular anastomoses is performed (Lee, Tung and Orloff, 1971). Sperm forming cells are probably not able to obtain sufficient oxygen or nourishment for survival from interstitial fluid when transplanted in the "free" state before a blood supply is formed, and consequently atrophy.

The whole graft was found to be atrophic in animals sacrificed 7 weeks after allotransplantation, and seminal vesicle weights were the same as those of purely castrated mice. Immunological rejection is likely to have been responsible, since immunosuppressive therapy was not employed in this group of experiments. Whether or not rejection of interstitial cells is delayed in the presence of endocrine "need" is being investigated, but from these experiments it is evident that at 7 weeks after grafting there was no evidence of them or of their activity.

Summary

Free transplantation of testis homogenates was performed in the mouse in autologous combinations.

Results were assessed histologically and by the effect on primary and secondary sexual characteristics.

While seminiferous tubules atrophied and no spermatogenesis occurred, interstitial cells survived.

In previously castrated animals transplantation was followed by normal seminal vesicle and penis development in adolescent mice and prevention of atrophy in adult animals.

These changes were not seen after allotransplantation, presumably due to graft rejection.

We are grateful to the Medical Research Council for supporting this work, to Dr Laurence Henry for assistance with histological studies and the photographic department of the Royal Hospital, Sheffield for the illustrations.

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Pauline, F. Boyle, BSc, Scientific Officer.

John C. Hammonds, FRCS, Registrar in Urology.

Short Case Report

Tuberculous Infection of a Serous Cyst of the Kidney

A youth aged 17 presented with 2 attacks of haematuria and right loin pain.

Investigations

Urine: pH 6 trace of protein 30 w.b.c.'s and occasional r.b.c.'s per h.p.f. **Blood E.S.R.** 11 mm in 1st hour (Wintrobe). w.b.c.'s 6,800 per cu mm. **Radiography:** I.V.P. showed a bulge of the renal outline over the middle third of the right kidney with deformity of the calyces (Fig. 1).

The right kidney was explored and found to contain a multilocular cyst of clear fluid. The roof was excised and the rim sutured.

Histological examination of the cyst wall (Fig. 2) showed it was lined with low cubicle epithelium with giant cells and epithelioid cells in a stroma of fibrous tissue.

Mycotuberculosis was cultured from the fluid and also from postoperative urine specimens.

He had been tuberculin positive at age 13, but a chest x-ray had been clear.

Comment

In the only similar case found described, the presentation was more acute and the cyst contained a litre of pus, in which tubercle bacilli were seen (Patel and Mallet-Guy, 1925).

I should like to thank Mr J. G. Gow for his advice in preparing this paper and Dr E. M. McConnell for her help with the histological examination.

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Orpington, Kent.

Reference

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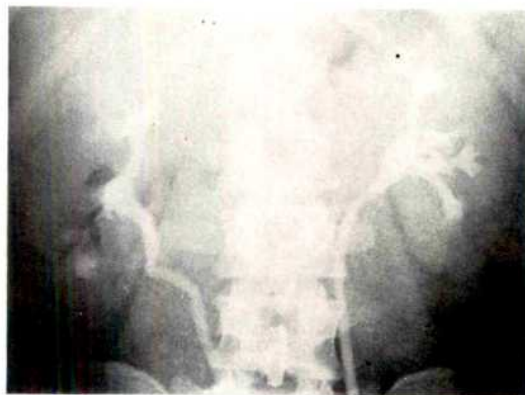


Fig. 1



Fig. 2

Discussion of Recent Papers

The Effect of Prostatectomy on the Symptoms and Signs of Benign Prostatic Hypertrophy. By J. E. CASTRO (1973, 45, 428-431).

Mr Roger Hole; I doubt if many were surprised that Mr Castro found that prostatectomy is a better treatment than placebo medication. But the design of the investigation, though probably unavoidable, is such that only patients that have *failed* to benefit from the placebo treatment were selected for this study. Unless this is borne in mind, it might be assumed that prostatectomy will *always* be a better form of treatment than placebo medication.

Many urologists will agree with Chapman (1949) and Badenoch (1962) that about one-quarter of the men who present with symptoms of "prostatism" short of acute or severe chronic retention will, if merely observed over a period of years, either lose their symptoms or suffer no progressive increase in these symptoms. Of course, placebo medication or any other medical or surgical treatment that is not positively harmful may perhaps augment this progress subjectively.

Perhaps another fifth of these men, if observed over a period of months, will deteriorate so that they then obviously require effective treatment—they would presumably do the same if they had been given a placebo: these will be the "placebo failures". Their natural history is clearly different from the preceding group—though the behaviour of any individual patient cannot always be reliably determined in advance of this period of observation.

Prostatectomy must carry more risk than placebo medication, so in this significantly large group of men whose prostatic symptoms will remain static or will regress, Mr. Castro's findings will not apply—for placebo medication must be better than unnecessary surgery. Of course, no medication at all might be even better for there would then be no risk of the urologist deceiving himself.

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References

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BADENOCH, T. L. (1962). Expectant treatment of benign prostatic enlargement. *Lancet*, 2, 684-688.

Castro; Many patients with benign prostatic hypertrophy respond to placebo medication. My own investigations show the symptom score of patients taking placebo for 6 months was less in 76%, frequency was less in 71% and nocturia in 62%. More surprisingly, signs which are considered more reliable than symptoms changed whilst patients were taking placebo. For example, digital prostate size was thought to be smaller in 15 out of 21 patients and radiological measurements of residual urine were significantly less. These changes must reflect the subjective element of such observations and perhaps question the reliability of the criteria used by many urologists in the assessment of their patients for operation.

The more important criticism, that only "placebo failures" were investigated in the study described, is not true. It was stated that after placebo there was improvement of mean symptom score, frequency and nocturia. In fact, symptom score improved in 6 out of 7 patients, there was less frequency in 5 and a decrease of nocturia in 3.

It may, therefore, legitimately be asked "why operate on these patients after placebo?" Despite improvements there were continuing symptoms (mean frequency 13.1) and variables, which are not influenced by placebo and hence probably more objective (flow rate, bladder pressure, residual urine measured by catheterization), continued to deteriorate.

The study described showed quantitatively that prostatectomy gave additional benefit to patients suffering the symptoms of B.P.H. that had previously improved after placebo and there was improvement of objective measurements that were not affected by placebo.

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Book Review

Immunopathology of the Renal Glomerulus. By F. G. GERMUTH and E. RODRIGUEZ. 1st Edition. Pp. 227 with 160 illustrations. Boston Mass. Little, Brown and Company. 1973. Price—not shown.

Diffuse parenchymal renal disease, though not strictly within the province of the urological surgeon, regularly features in the differential diagnosis of silent haematuria and proteinuria. Glomerulonephritis in its various forms accounts for the great majority of cases of diffuse glomerular injury which may present for diagnostic consideration. The authors, Dr Germuth, a pathologist, and Dr Rodriguez an immunochemist, have written a beautifully and liberally illustrated book which sets out to explain in considerable depth the principle immunological and pathological mechanisms of the glomerular damage in glomerulonephritis and other forms of immunologically determined glomerular injury. They have employed a combination of light microscopy, immunofluorescence microscopy, and electron microscopy to study material obtained from experimental models of glomerulonephritis in laboratory animals, as well as a large number of renal biopsies taken from patients with glomerulonephritis. They confirm, convincingly and elegantly, the generally accepted view that most glomerulonephritis is caused by deposition within the glomerular capillaries of soluble and freely circulating antigen-antibody complexes. Immunoglobulins and complement can be accurately identified along the glomerular walls by immunofluorescent techniques and the exact position of the deposits can be localised by electron microscopy. They show that by a combination of clinical and biochemical examination and detailed histological study of renal biopsy material it is becoming possible to distinguish reliably the different entities which are emerging within this group of diseases. Detailed consideration is given to the mechanism of glomerular damage in association with the collagen diseases, and throughout the book they have stressed the importance of clinical and pathological correlations. A case is made for the use of immunofluorescent staining techniques to distinguish forms of glomerulonephritis which are likely to be rapidly progressive from those which are likely to be self-limiting. Finally a courageous attempt has been made to construct a classification of glomerulonephritis which takes account of the site and identity of the immunological process. The excellent quality of the photomicrographs and the clarity of the discussion makes the book a valuable review of the present state of knowledge in this rapidly developing field.

P. R. U.

Conferences and Courses

RHODESIAN UROLOGICAL ASSOCIATION

The 10th Biennial Congress of the Urological Association of South Africa will be held under the auspices of this Association from 8th to 14th September 1974 at the VICTORIA FALLS and WANKIE GAME RESERVE.

Fuller Details From:

RAYMOND WEINBERG, FRCS

Lancet House,

24 North Avenue,

Salisbury,

Rhodesia

ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE*

Acta Urologica Belgica

By VICTOR LANE

"The Silent Kidney." J. RAGER. (1973, **41**, 189-324.)

—The entire issue is given over to this problem. Diagnostic means are dealt with under the following headings—radiological investigations, isotope studies, scanning and renal biopsy. It is pointed out that 10% of patients have a reaction of some sort following an intravenous urogram, with 1 death in each 125,000 examinations. In the second part, the aetiology of the silent kidney is dealt with under these headings—congenital anomalies, vascular lesions, lesions destroying the renal parenchyma, and obstructive lesions. In a short final section, the criteria for recovery of function are discussed.

American Journal of Roentgenology

By M. H. DEVEREUX

"Column of Bertin: Diagnosis by Nephrotomography." W. M. GREEN, B. D. PRESSMAN, B. L. MCLENNAN and W. J. CASARELLA. (1972, **116**, 714-723.)—The radiological features of a column of Bertin are described. When enlarged the column may be mistaken for a tumour, as in partial duplication, but the pyelographic features are typical and arteriography usually unnecessary.

"Acute Renal Carbuncle. The Roentgenographic Clarification of a Medical Enigma." J. G. RABINOWITZ, M. N. KINKHABWALA, T. ROBINSON, E. SPYROPOULOS and J. A. BECKER. (1972, **116**, 740-748.)—Six cases of this uncommon condition are reported. It is an increasing problem in the USA due to drug addicts "main-lining". Clinically the disease often presents insidiously. Radiologically there is usually a space-occupying lesion in the kidney associated with a perinephric abscess. Poorly filled vessels pass through the lesion on arteriography.

"Renal Angiography in Patients with Haematuria." K. JONSSON. (1972, **116**, 758-765.)—Angiographic studies in patients with haematuria who have a normal I.V.P. and cystoscopy reveal the occasional hypernephroma and a far higher yield of renal vascular anomalies than shown in previous studies.

"Unilateral Total Renal Dysplasia in Children." L. NEWMAN, K. SIMMS, J. KISSANE and W. H. MCALISTER. (1972, **116**, 778-784.)—Renal dysplasia is the commonest cystic disorder of the kidney in childhood and the commonest cause of an abdominal mass in the newborn. This good review correlates the many names by which this condition was formerly known.

"The Elusive Ectopic Ureteroceles." G. W. FRIEDLAND and J. CUNNINGHAM. (1972, **116**, 792-811.)—This is an excellent review of the embryology, pathology, clinical features and radiology of ectopic ureterocoele. Illustrations of the radiological features are numerous and difficulties in making the diagnosis are discussed.

"Urethral Tumors." P. H. ARGER and J. L. STOLZ. (1972, **116**, 812-821.)—The history of the radiology of ureteral tumors is presented, followed by a well-illustrated presentation of the radiological features and problems of this uncommon condition.

"Cowper's Glands in the Urethrogram." G. CURRARINO and F. FUQUA. (1972, **116**, 838-842.)—Radiological demonstration of Cowper's glands or ducts in the absence of distal urethral strictures and urethral diverticula is rare. Ten such cases, mostly children, are presented. The dilated ducts are presumed to be a congenital anomaly as no obstruction or infection was present.

"Hypernephromas with Massive A-V Fistulas." T. J. SONDAG, S. K. PATEL, J. P. PETASNICK and J. CHAMBLISS. (1973, **117**, 97-103.)—Four cases are reported only 1 of which had heart failure. The radiological features are well illustrated. The cause is thought to be erosion by tumour of a large artery and vein at the hilum of the kidney rather than the presence of shunting vessels in the tumour itself.

"Angiophotomography and Subtraction. Relative Value in Renal Mass Lesions." C. A. ATHANASOULIS, E. A. DOUGLAS, S. NAVANI, E. J. FERRIS and J. H. SHAPIRO. (1973, **117**, 108-111.)—A technique is presented by which a renal mass which is not obviously a vascular carcinoma on selective angiography can be diagnosed. Tomography is combined with selective renal angiography. Selected films are submitted to second order photographic subtraction which removes extraneous shadows. The method is useful for evaluating spurs, the thickness of the wall of a lesion and showing tumour vessels not seen on ordinary films.

"Evaluation of Ultrasonic B-mode Scanning in the Diagnosis of Renal Masses." V. L. DOUST, B. D. DOUST and H. C. REDMAN. (1973, **117**, 112-118.)—The criteria for diagnosing renal cysts by ultrasound are discussed in detail. The technique cannot detect lesions smaller than 2-3 cm diameter. The authors suggest that ultrasound could replace angiography in the initial assessment of renal masses, providing that cysts were aspirated and solid lesions explored.

"Ultrasonic Diagnosis of Wilms' Tumors." R. HÜNIG and J. KINER. (1973, 117, 119-127.)—This is a good paper presenting in detail the ultrasound characteristics of Wilms' tumour. The tumour consists of an extensive echo-free zone with scattered echoes within it possibly due to areas of necrosis. The tumour is not distinguishable from normal renal parenchyma.

"Genito-urinary Complications of Granulomatous Bowel Disease." R. J. BAGBY, J. L. CLEMENTS, Jr., T. W. PATRICK, J. V. ROGERS and H. S. WEANS. (1973, 117, 297-306.)—This paper presents 9 cases of Crohn's disease with involvement of the urinary tract. The Crohn's disease is usually severe and of long standing. The alimentary tract dominates the clinical picture and urinary symptoms may be minor. Fistula formation between the ileum and bladder is the commonest disorder and usually presents with cystitis and pneumaturia. The fistula cannot usually be demonstrated radiologically and is best diagnosed by cystoscopy. Renal complications such as uric acid calculi secondary to chronic diarrhoea can occur as well as the more obvious complications in the urinary tract due to sepsis.

"Seminoma of the Testis." V. S. SAXENA. (1973, 117, 643-652.)—The results of treatment of 75 cases of seminoma of the testis are presented. Retroperitoneal lymphadenectomy was used early on but has now been abandoned in favour of simple orchidectomy and radiotherapy alone as in the UK. The results are as good as in our recent Royal Marsden series with 100% cure in Stage I disease. Irradiation of the mediastinum and neck was used more often than in the UK but they conclude that it is unnecessary in Stage I seminoma.

"Supervoltage Radiation Therapy of the Testicular Tumors." J. D. EARLE, M. A. BASHAW and K. S. KAPLAN. (1973, 117, 653-661.)—This report from the Stanford Division of Radiation Therapy presents excellent results in the treatment of seminoma by simple orchidectomy and radiotherapy alone. Their system of staging is odd by British standards and teratomata are referred to as carcinomata with no further subdivision. Lymphadenectomy is routine in the treatment of the "carcinomata" and the paper tries to assess whether this should be before or in between courses of radiotherapy, their "Sandwich Treatment". Survivals do not appear to be better than in the UK with simple orchidectomy and radiotherapy alone.

"Haemorrhagic Cystitis and Vesico-ureteral Reflux Secondary to Cytotoxic Therapy for Childhood Malignancies." W. A. RENERT, W. E. BERDON and D. H. BAKER. (1973, 117, 664-669.)—Two cases of cyclophosphamide cystitis and 1 due to cytosine arabinoside (the first to be reported) are presented. Reflux is due to fibrosis involving the vesico-ureteric mechanism.

"A Simplified and Reliable Cannulation Technique for Lymphography." J. F. BERGSTROM. (1973, 117, 701-703.)—Those performing lymphography will benefit from studying this paper as the method described seems much more simple than many currently in use.

"Fetal Renal Hamartoma—A Benign Tumour to be Distinguished from Wilms' Tumour." W. E. BERDON, H. J. WIGGER and D. H. BAKER. (1973, 118, 18-27.)—Three cases of renal hamartomata are reported, 2 in neonates, the third in a 2-month-old infant. Hamartomata in children cannot be distinguished clinically or radiologically from Wilms' tumour. Hamartomata, however, have a benign course and radiotherapy and chemotherapy are not required after nephrectomy. Histologically many hamartomata look like well-differentiated fibrosarcomata and the authors support the view that neonatal renal fibrosarcomata are not differentiated Wilms' tumours but are in fact hamartomatous malformations of the kidney.

"Roentgenologic Sequelae of Neonatal Septicaemia and Urinary Tract Infection." T. R. WELCH, M. B. NOGRADY and E. W. OUTERBRIDGE. (1973, 118, 28-38.)—The growing kidney is particularly vulnerable to infection and this paper from Montreal presents evidence that the neonatal kidney is particularly vulnerable. All of the cases of septicaemia were due to Gram-negative infections and seemed to originate in the urinary tract. Renal scarring and impairment of renal growth was demonstrated to occur in a matter of months. The authors postulate that the cause of a shrunken kidney in an adult, a not uncommon incidental finding on urography, may be infection during the neonatal period.

"Neurofibromatosis and Renovascular Hypertension in Children." E. MENA, J. J. BOOKSTEIN, J. F. HOLT and W. J. FRY. (1973, 118, 39-45.)—This paper from Ann Arbor reports 5 cases of renovascular hypertension in children with neurofibromatosis. All were shown to have renal arterial stenosis and the 4 cases subjected to surgical treatment became normotensive. Pheochromocytoma is another cause of hypertension in patients with neurofibromatosis.

"Magnification Digital Roentgenography: A Method for Evaluating Renal Osteodystrophy in Haemodialysed Patients." L. CALENOFF and J. NORFRAY. (1973, 118, 282-292.)—The development of osteodystrophy in dialysed patients is common and may be due to the dialysate having too low a concentration of calcium or the development of hyperparathyroidism. Early diagnosis is important and the authors describe a new radiological method which is less time-consuming and less expensive than methods currently in use.

"Bone Changes Following Uretero-Ileostomy." E. J. LEWIN and D. F. FRANK. (1973, 118, 347-355.)—Two cases of rickets in children with ileal conduits are reported in this paper. Both had exstrophy of the

bladder and were diverted initially with uretero-colic anastomoses until renal deterioration necessitated revision to ileal conduits. Both loops were unsatisfactory, one being too long the other stenosed. One case developed bone changes before revision. The title is thus a little misleading.

Annals of Surgery

By J. E. A. WICKHAM

"Primary Dissecting Aneurysms of Renal Artery."

J. J. KAUFMAN, W. F. COULSON, J. W. LECKY and G. POPJACK. (1973, 177, 259-263.)—This paper reports on an isolated case of dissecting aneurysm of the renal artery with spontaneous re-entry producing resolution of the patient's renovascular hypertension. This problem was treated by resection of the diseased vessel and substitution by a Dacron graft. This resulted in normal renal function and normotension. The problem of renal artery dissection is discussed and it is suggested that the aetiology of some cases of dissection may be due to a medial fibroplasia.

"Traumatic Renal Artery Thrombosis."

D. G. SKINNER. (1973, 177, 264-267.)—The paper reports on 1 case occurring after a road traffic accident. Non-function of 1 kidney was seen on pyelography shortly after the accident and this encouraged exploration of the kidney. A clot was extracted from the main renal and main branch arteries and the patient made a good postoperative recovery. The importance of early diagnosis is emphasised. Local excision of the injured segment of artery is suggested followed by vein graft replacement. Cold perfusion of the kidney during the procedure is recommended.

"Wound Complications in Recipients of Renal Transplants."

T. ROBERT and M. D. SCHWEITZER. (1973, 177, 58-62.)—This is a paper discussing 30 septic wound complications occurring in 178 renal transplant recipients. The most usual cause of wound sepsis was haematoma associated with the transplant operation. It is suggested that measures to reduce the incidence of septic wound complications should be the avoidance of drains, carefully managed regional anticoagulation regime if haemodialysis is required and the use of local antibiotics. Wound haematomas are best managed by evacuation and primary wound closure without drains. Transplant nephrectomy should be performed early before the rejected graft becomes septic. Lymphoceles when they occur should be treated by the insertion of Penrose drains and can be prevented by the ligation of divided lymphatics.

The Australian and New Zealand Journal of Surgery

By H. H. PEARSON

"The Use of Trimethoprim-Sulphamethoxazole in the Treatment of Complicated Urinary Tract Infec-

tion." STUART SILLAR. (1972, 41, 368-371.)—The author while with the Urological Department of the Meath Hospital and County Dublin Infirmary carried out a clinical trial with trimethoprim-sulphamethoxazole on 50 patients with established urinary infection. There were 27 males and 23 females and many had organic pathology of a chronic nature. They were divided into 4 groups. Group A (14 patients) had infection without associated pathology. Group B (12 patients) had a chronic infective lesion. Group C (12 patients) had an obstructive uropathy. Group D (12 patients) had calculi or tumour. The organisms were *E. coli*, *Proteus vulgaris*, *Streptococcus faecalis*, *Klebsiella aerogenes*, and *Pseudomonas*. Ten patients had mixed infections. Of the 51 patients, 31 showed complete symptomatic relief, 17 were improved and 3 were no better. 31 cultures became sterile, 5 developed new organisms and 14 showed persisting infection. The results with individual organisms are classified and there was an overall cure rate of 62%. He concluded that the synergistic action of trimethoprim-sulphamethoxazole is very effective in the treatment of complicated urinary tract infections.

"Spontaneous Urinary Extravasation: The Problems of Diagnosis and Management."

DAVID J. ELLIS. (1972, 41, 371-374.)—The author from the Repatriation General Hospital, Heidelberg, Victoria, reports a 72-year-old male patient, who had been treated with steroids for rheumatoid arthritis since 1965, and who suddenly developed a spontaneous extravasation of urine from the upper group of calyces of the right kidney. The condition responded to antibiotic therapy. The films suggest that extravasation may have occurred as a result of a papillary necrosis, and the patient had been on salicylates and other analgesics for a long period. The author discusses the literature on the subject and points out that there are 2 clinical entities—(i) spontaneous extravasation of urine during intravenous urography performed during or soon after an attack of renal colic and (ii) spontaneous rupture of the renal pelvis and ureter. The first is usually relatively benign and the second may be dangerous. Full investigation and follow-up are mandatory.

"A Case of Aortic Aneurysm with Bilateral Ureteric Obstruction."

PAUL KITCHEN and PETER J. MORRIS. (1972, 42, 126-128.)—The authors from the Royal Melbourne Hospital, Victoria, present a patient with bilateral ureteric and vena caval obstruction due to retroperitoneal fibrosis associated with an abdominal aortic aneurysm. Partial resection of the aneurysm and insertion of a Dacron graft resulted in regression of the ureteric and caval obstruction. They suggest that freeing of the ureters at the time of operation for the aneurysm as is generally advocated is time consuming and probably unnecessary. The authors consider too that leaking aneurysms may be responsible for many cases of unexplained retroperitoneal fibrosis.

"Functional Hydroureteronephrosis Associated with Prostatitis and Urinary Infection: Report of a Case."

S. K. SHARMA, M. S. RAO, B. V. R. RAJU, I. R. RAO and S. M. SINGH. (1972, **42**, 181-182.)—From the Department of Urology, All-India Institute of Medical Sciences, New Delhi, the authors report an adult patient with non-obstructive hydroureteronephrosis occurring as a result of relative ureteral atony in the presence of urinary infection. The patient, a 65-year-old male had a congestive prostatitis with a urinary infection. Although the blood urea was normal an excretory urogram showed bilateral hydronephrosis with tortuosity and dilatation of both ureters. There was no reflux. Treatment with chemotherapy alone resulted in a sterile urine and complete regression of the bilateral dilatation. They conclude that the presence of an insignificant amount of residual urine in combination with symptoms of prostatism and a radiologically demonstrated dilated upper tract should alert one to the possibility of these phenomena being of infective rather than of obstructive origin.

"Intravenous Pyelography before Prostatectomy: An Evolution of Its Use."

W. J. BOEREMA. (1972, **42**, 35-38.)—From the Royal Perth Hospital, Western Australia, the author analysed 125 intravenous pyelograms performed before open prostatectomy for benign prostatomegaly. He described the obvious pre-operative mandatory investigations such as haemoglobin estimation, cross matching, renal function tests and micro-urines but queries the necessity of pre-operative pyelograms. Of the 125 patients 57% presented with acute retention, 39% with chronic symptoms and 4% with haematuria. A review of the intravenous pyelograms showed that 104 of the 125 films were normal. The 21 abnormal films showed 2 with a non-functioning kidney, 1 with a staghorn calculus, 3 with space occupying lesions, 2 with congenital abnormalities, 4 with bilateral back pressure, 4 with unilateral back pressure, 3 with bladder calculus, 1 with a bladder diverticulum and 4 with bladder filling defects, all of which turned out to be of no significance. In no case was any additional treatment performed except the removal of bladder calculi. He concludes that the preoperative pyelography is probably unnecessary especially where there is an indwelling urethral catheter and that such investigation could be postponed to a postoperative study where there are clinical indications.

"Renal Trauma in Children: A ten year review."

IAN S. REID. (1973, **42**, 260-266.)—The experience of renal trauma at the Royal Children's Hospital, Melbourne, is analysed. 78 children were involved over the 10-year period. Nunns classification (1962) into contusion (type 1), cortical lacerations (type 2), calyceal lacerations (type 3) and complete tears (type 4) was extended to include a fifth type where the main damage was to the renal vessels. The clinical features and the radiological and operative findings were used to classify the lesions. Falls and motor vehicle accidents were the most common causes of injury.

Examination of methods of management indicates that in types 1 and 2 conservative treatment is usually sufficient; in type 3 initial non-operative treatment is indicated but long-term follow-up is necessary; in type 4 injuries and those with vascular lesions the need for early diagnosis is important and included renal angiography. These patients require early surgical intervention. The author suggests that in patients so treated there are prospects of saving renal tissue and reducing morbidity.

The British Journal of Radiology

By CHARLES NICHOLAS

"Renal Cortical Abscess, Perinephritis and Perinephric Abscess in Diabetes."

K. C. SIMPKINS and N. C. BARRACLOUGH. (1973, **46**, 433-436.)—The Leeds General Infirmary radiodiagnostic department report their findings in 3 cases and emphasise that renal cortical inflammation proceeding to perinephritic abscess is more common in diabetics, and is difficult to diagnose and is often fatal. Plain X-rays show loss of renal outline, obliteration of the lateral border of the psoas, scoliosis, basal pleurisy, restricted diaphragmatic movement and sometimes gas within the kidney, ureter or perinephric space. The kidney may be rotated or displaced and the renal pelvis and ureter compressed. A localised cortical abscess causes displacement and compression of the calyces in the I.V.P. and its outline can be demonstrated by tomography. The thickness of the abscess wall distinguishes it from renal cyst but not from a breaking down neoplasm. Renal angiography was considered to be unhelpful. The radiological findings in all 3 cases were confirmed postmortem.

Deutsche Medizinische Wochenschrift

By JOHN GRIEVE

"Ultrasonics in Renal Diagnosis."

H. LUTZ and G. RETTENMAIER. (1973, **98**, 361-364.)—Using 2-dimensional ultrasonic scanning with a picture frequency of 16 per second these authors from Nurnberg claim much help from this technique. The depth and respiratory movement are easily determined and the pelvis and parenchyma demarcated. Congenital small kidney may be differentiated from a pathological small kidney and different types of hydronephrosis recognised. In addition stones and renal tumours are picked up. No mention is made of any risk to the patient as a result of exposure to ultrasonics.

"Changes in the Human Testis during Anti-androgen Treatment."

F. STÄDTLER and H. J. HORN. (1973, **98**, 1013-1019.)—In 33 patients 77 bilateral testicular biopsies were examined before and after treatment

with cyproterone acetate. Tests included histology, histometrical examination and enzyme histochemistry. After treatment sperm formation is reduced in some cases to maturation arrest at the spermatocyte stage and this appears to be related to dosage. There is also a decrease in the mean tubular diameter. In 3 of the patients there was evidence of quite severe gonadal damage before treatment. A gradual reduction in the dose of anti-androgen was followed by recovering spermatogenesis suggesting that cyproterone acetate produces no permanent testicular damage.

"High Renal Ectopia: Etiology Classification and Diagnosis." F. SCHREITER and R. ARNGWERD. (1973, **98**, 1169-1175.)—High renal ectopia represents the thoracic kidney and in 3 patients with this anomaly observed in a 9-year period all were suspected of having a lung tumour. There are 3 forms of the condition:

1. Primary which requires no treatment.
2. Secondary. Congenital with either a false diaphragmatic hernia or a flaccid diaphragm. This only requires treatment when there is pressure on heart or lungs.
3. Traumatic. This normally requires surgical correction.

This is a very uncommon usually symptomless anomaly which may cause problems in diagnosis.

"Prolonged Demonstration of Spermatozoa after Vasectomy." D. KONIETZKO and F. REINECKE. (1973, **98**, 1221-1223.)—Sperm counts were performed in 40 patients after vasectomy and only 15 had azoospermia. 6-8 weeks later the other 25 showed necrospermia and this continued for prolonged periods. The authors believe that vasectomy cannot be considered successful till azoospermia is achieved and this may take a long time.

La Nouvelle Presse Medicale

By JOHN GRIEVE

"Torsion of the Spermatic Cord in the Adult: an Emergency too often misdiagnosed." L. B. GIBOD, C. OLIER and A. STEG. (1972, **1**, 3063.)—In a period of 18 years ending in 1972, 29 out of 58 cases of torsion of the testicle occurred between the ages of 21 and 61. The chief cause of confusion was epididymo-orchitis and trauma. In 4 patients operated on within 10 hours of onset recovery was complete while in 5 with recurring milder symptoms bilateral orchidopexy was followed by permanent recovery. Atrophy occurred in all cases where operation was delayed beyond 24 hours.

"Teratospermia in Patients with Varicocele." F. CZYGLIK, G. DAVID, J. P. BISSON, P. JOUANNET and C. GERNIGON. (1973, **2**, 1127-1130.)—Seminal analyses were done on 80 patients, 50 of whom were sterile and

had varicoceles, 20 of whom were sterile without varicoceles and 10 of whom were fertile and had no varicoceles. In the patients with varicoceles the sperm morphology was altered. Teratospermia was over 50% and elongated or narrowed heads in over 20%. The middle pieces were frequently abnormal in association with abnormal heads. The authors suggest that the role of the varicocele relates to the production of teratospermia.

"Milk of Calcium Renal Disease." A. MURISASCO, A. MOSTEFA, F. BARNOUIN, J. POLLINI, L. AUBERT, J. PADOVANI and M. KASBARIAN. (1973, **2**, 1765-1768.)—These workers from Marseille and Toulon have found only 23 cases of "milk of calcium disease" (so described by Howell, 1960). In this condition there is a cavity in the kidney which may communicate with the pelvis or it may not. This contains a milk which sediments to the most dependent part of the cavity. The authors describe 3 cases they have seen and emphasise the importance of radiography (plain film) in the erect position in cases of stone.

Surgery, Gynaecology and Obstetrics

By THOMAS MOORE

"What's New in Surgery: Urology." ABRAHAM T. K. COCKETT. (1973, **136**, 219-220.)—This review of very recent urological literature refers to work on (1) experimental bladder tumours produced in rats by a nitrofur derivative and the mechanisms of immunity, (2) the isolation of ribonucleic acid virus from 3 papillary tumours of the renal pelvis in humans, (3) diethylstilboestrol induced renal carcinomata in hamsters and then treated by hypophysectomy and bilateral adrenalectomy, which proved inhibiting and drugs like cortisone which accelerated growth, (4) the use of microvascular techniques to repair the renal artery or its branches in renal transplantation, (5) the use of methylprednisolone in lysosomal enzyme release and vascular resistance in the isolated perfused dog kidney, (6) transformed lymphocytes in the rejecting dog kidney allograft, (7) the effects of testosterone on the rat testes, (8) radioactive scanning of kidneys as a measure of blood flow, (9) the dissolution of urinary calculi by an ultrasound technique. As usual the value of this review is very much diminished by the absence of detailed references.

"Renal Trauma in Children." N. JAVADPOUR, PATRICK GUINAN and IRVING M. BUSH. (1973, **136**, 237-240.)—From the Department of Urology of the Chicago Medical School the authors analyse results of 110 cases of renal trauma in children up to the age of 16 years. The youngest patient was 3 years old. 79 patients were male; the cause in 40 was a fall, in 29, road traffic accident, in 26, stab wounds, in 8 gun-shot wounds and in 7 the cause was unknown. They stress the importance of intravenous pyelography in diagnosis and programming of treatment; when necessary retrograde pyelography and arteriography, sometimes

even at operation, are useful. 32 required operation; 8 nephrectomy, 10 partial nephrectomy, drainage in 6, débridement in 3 and repair in 5. The authors stress that the early clamping of the renal pedicle is essential to conservative surgery.

"Urinary Tract Calculi after Intestinal Shunt Operations for the Treatment of Obesity." STEPHEN S. DICKSTEIN and BOY FRAME. (1973, **136**, 257-260.)—From the Henry Ford Hospital, Detroit, the authors have studied 34 patients suffering from extensive obesity treated by jejunio-ileostomy or jejunio-colostomy bypass operations. 32.4% developed renal calculi, usually consisting of calcium oxalate; the complication was commoner in the jejunio-colostomy cases. They discuss the biochemistry of oxalate formation in the normal and in patients having had one of these operations. Although the 24-hour urinary output of oxalate is usually increased after these operations, the authors do not believe it is the only factor as the stones did not always form in those with the high oxalate output.

"Renovascular Hypertension in Patients with a Solitary Kidney." JOSEPH J. KAUFMAN and ANDREI N. LUPU. (1973, **136**, 395-400.)—From the Department of Urology of the UCLA School of Medicine, Los Angeles, the authors present detailed reports of their 9 patients with solitary kidneys who suffered from renovascular hypertension. These cases bring the total reported in the world literature to 32. They stress that a variety of surgical treatments are necessary and the technique must be carefully selected for each patient. Generally at present, the main indications used are hypertension, abdominal bruit and angiographic evidence of renal artery stenosis. The value of plasma renin activity in such patients is not reliable. In their view surgical treatment offers a good prospect for cure and because of the high risk of arterial thrombosis in these cases, medical treatment in patients fit for surgery is not recommended.

"Surface Potassium Ion Activity of the Ischaemic Kidney." FRANK E. DEUVAERT, GEORGE M. WATKINS, JAN R. DMOCHOWSKI and NATHAN P. COUCH. (1973, **136**, 429-432.)—In the Harvard Medical School and the Peter Bent Brigham Hospital, Boston, the authors have studied the extracellular fluid potassium concentration on the renal surface in the *in vivo* normothermic kidney rendered ischaemic; they have shown an 8-times normal rise after 45 minutes and 13-times normal after 120 minutes. After reflow is established the concentration of potassium returns to control values after 15 minutes after the shorter ischaemia interval and 30 minutes after the longer. It was not possible to determine how much of the potassium returned to the intracellular space. The surface potassium ion-selective electrode proved a useful device for study of tissues and organs *in vivo*.

"The Fate of the Renal Transplant with Delayed Function." JOHN R. WHITTAKER, FRANK J. VEITH,

ROBERT SOBERMAN, PARVIZ LALESARI, IAN TELLIS, SELWYN Z. FREED and MARVIN L. GLIEDMAN. (1973, **136**, 919-922.)—In a retrospective study of 54 cadaver renal allograft recipients, the authors working at the Medical Centre and Albert Einstein College of Medicine, New York, have shown that the immediate urine secretion at the time of transplant resulted in a significantly better survival rate at 3, 6, 12, 24 and 36 months. Many grafts failing immediately to produce urine had a short ischaemic period suggesting other factors, possibly an immunological rejection response in spite of good tissue typing and cross-match. They have also demonstrated that the extra investigations and treatment in such cases contribute significantly to the poor final result.

"Renal Blood Flow during Endotoxin Shock in the Subhuman Primate." JOHN P. SELMYER, DAVID G. REYNOLDS and KENNETH G. SWAN. (1973, **137**, 3-6.)—Experimental studies of endotoxin shock in baboons carried out by the authors at the Walter Reed Army Institute of Research, Washington, have shown a fall in renal blood flow and renal vascular resistance. Histological examination of kidneys after 4 hours has demonstrated the presence of microthrombi in the glomeruli, necrosis of proximal tubular epithelium and an eosinophilic transudate in proximal and distal tubules. From these results it seems likely that the renal ischaemia in baboons, contrary to that observed in the dog from the same endotoxin, is due to the fall in perfusion pressure.

"The Fate of Failed Renal Homografts Retained after Retransplantation." ÅKE GUSTAFSSON, CHARLES G. HALGRIMSON, ISREAL PENN and THOMAS E. STARZL. (1973, **137**, 40-42.)—The authors, from a well-known Transplantation Centre in Denver have studied unsatisfactory renal homografts which were left *in situ* after a further transplantation. One patient died from septicaemia secondary to necrosis and infection of a retained intra-abdominal graft. Symptoms developed in 3 other patients with extraperitoneal pelvic grafts but were cured by nephrectomy. The authors suggest that extraperitoneal grafts may be left *in situ* provided that there is careful follow-up for evidence of necrosis or infection. Elective nephrectomy may have to be carried out later or never become necessary.

"Anatomic Variants of the Urachus Related to Clinical Appearance and Surgical Treatment of Urachal Lesions." MOGENS BLICHERT-TOFT and OLE VAGN NIELSEN. (1973, **137**, 51-54.)—The authors working in Copenhagen, dissected 81 bodies of all age groups and described 4 anatomical variations based on the course of the urachus in relation to the obliterated umbilical artery, its length and the extent of its epithelial lining. They report a series of 8 patients with acquired urachal disease.

"Clearance Rate and Renal Effects of Stroma-free Haemoglobin on Acidotic Dogs." MICHAEL RELIHAN

and MARTIN S. LITWIN. (1973, **137**, 73-79.)—In the experimental work carried out by the authors in the Tulane School of Medicine, New Orleans, by the administration of ammonium chloride, 2 groups of dogs were rendered acidotic. One group of these was infused with normal saline and the other with a stroma-free haemoglobin solution. No toxic effect on the kidney by the haemoglobin solution could be demonstrated. During the first 6 hours after infusion, 47% of the haemoglobin was excreted in the urine and another 14% during the following 18 hours. 20-30% more of the pigment was excreted as meth-haemoglobin than was present in the infused solution. Histology of the lungs, liver, kidneys and repeat urinalysis demonstrated no difference between the controls and those infused with haemoglobin.

"Improved Cadaveric Nephrectomy for Kidney Transplantation." SELWYN Z. FREED, FRANK J. VEITH, VIVIAN TELLIS and MARVIN L. GLIEDMAN. (1973, **137**, 101-103.)—The authors describe the technical details of a method which they believe results in donor kidneys with adequate vessel length which are much easier to transplant.

"The Role of Surgery in Sickle Cell Disease." M. WAYNE FLYE and DONALD SILVER. (1973, **137**, 115-126.)—This is a collective review of the subject from the Surgical Department of Duke University Medical College in Durham USA. The references to the effects of the disease in the genito-urinary tract are useful.

Der Urologe

By JOHN GRIEVE

"Fertility in Unilateral Cryptorchidism." H. MADERSBACHER, S. KÓVESDI and J. FRICK. (1972, **11**, 210-212.)—Fertility investigations were carried out by these workers from Innsbruck in 36 patients who had orchidopexy done for unilateral cryptorchidism. Of these 9 had a normal seminal analysis, 9 normal apart from a reduction in motility and 18 were definitely abnormal. In 31 of the patients the operation was done after the age of 10 and the authors believe that the results in these patients indicate the potential of the normally descended testis only. The results in general agree with those of most authors who have found a high incidence of infertility in unilateral cryptorchidism.

"The Rhythm of the Contractions of the Renal Pelvis." E. HAJÓS. (1972, **11**, 324-325.)—This report from Budapest is concerned with the image intensifier cineradiography of the renal pelvis in 800 patients. The rhythm of the contractions varied a great deal and there was no pattern about the variations. Quite frequently the variations were similar in both renal pelves when these were observed simultaneously. The normal subject shows as much variation as the patient with disease. The author believes that the

level of diuresis has some bearing on the rhythm of the contractions and suggests the possibility of some central influence or control. It is unfortunate that the author makes no reference to the work already done in this field.

"The Problem of Distal Urethral Abnormality in Girls." J. FRICK, H. MADESBACHER and H. PUSCHBAN. (1972, **11**, 330-332.)—In this paper from Innsbruck the authors discover no clear reason for distal urethral stenosis in girls. It may be a congenital abnormality or it may be secondary and temporary in relation to illness. Among 74 girls with this type of change recurrent pyuria was found and this was treated by long-term chemotherapy.

"Examination of the Epithelium of the Human Urinary Bladder by Scanning Electron Microscopy." D. SKOLUDA, K. WEGNER and I. RICHTER. (1972, **11**, 338-340.)—In Mainz the surface epithelium of the human urinary bladder was studied by scanning electron microscopy. Age and chronic obstruction without infection produced little change in contrast to fibrinous cystitis which caused widespread change. There may be a relationship between the fibrinous covering and the contraction mechanism of the bladder. The surface changes in the infected bladder prevented elimination of bacteria during voiding.

Urologia Internationalis

By JOHN GRIEVE

"The Anatomy and Physiology of the Ureterovesical Junction—a Prevesical Ureteric Sphincter." S. GIL VERNET. (1972, **27**, 310-335.)—This study from Barcelona describes a prevesical ureteric sphincter composed of fine circular muscle fibres situated just external to the bladder wall. From this longitudinal fibres continue through the bladder wall. These fibres have been shown in the neonate, the young child, the adult and the older patient. These fine fibres spread on to the detrusor and do not reach the trigone or the verumontanum. The author postulates that urine is propelled by ureteric peristalsis through a relaxed prevesical sphincter which contracts thereafter to prevent reflux. He links this with the episodic nature of ureteric discharge of urine.

Urologija I Nephrologija

By VICTOR LANE and ANTON PYTEL

"Reversible Hepatic Dysfunction in Patients Suffering from Renal Carcinoma." A. YA. PYTEL. (1973, **1**, 13-18.)—In the author's series of 11 cases, this occur-

red in 16.2%. It is an early manifestation of renal carcinoma and in the absence of metastases will return to normal after nephrectomy. As it may be for some time the only sign of the renal lesion, investigations to exclude a renal neoplasm should be carried out in all otherwise unexplained patients showing impaired kidney function.

"Clinical Assessment of Haematuria in Closed Renal Injuries." E. M. USTIMENKO. (1973, 1, 29-34.)

—Reviewing a series of 421 cases, it is concluded that the degree of haematuria is not itself an indicator of the severity of the renal damage nor is there any correlation between the severity of the renal injury

and the duration of the haematuria. The most common reason for the absence of haematuria in closed renal trauma is the anuria which results from associated injuries; haematuria may also be absent at first when the function of the injured kidney is temporarily arrested—in such cases, urine at first reaches the bladder only from the intact kidney but haematuria may set in later, as the function of the injured kidney returns to normal—this situation was found in 28 patients. The onset of haematuria may also be delayed by the blocking of the ureter of the injured kidney by a blood clot—this occurred in 5 patients. In 38 patients there was bilateral renal trauma with bleeding from each side.

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